Reaction Integration Using Electrochemically Generated Cationic Species(Dissertation_全文)

AUTHOR(S):

Ashikari, Yosuke

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Yosuke Ashikari

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Preface

The studies presented in this thesis have been carried out under the direction of Professor Jun-ichi Yoshida at the Department of Synthetic Chemistry and Biological Chemistry of Kyoto University during 2007−2013. The studies are concerned with reaction integration using electrochemically generated cationic species.

The author would particularly like to express his sincerest gratitude to Professor Jun-ichi Yoshida for his kind guidance and valuable discussions throughout this work. The author appreciates the circumstance to investigate in the field of the chemistry. The author is greatly indebted to Professor Seiji Suga of Okayama University for his fruitful consultation and valuable discussions. The author deeply appreciates to Associate Professor Toshiki Nokami of Tottori University for his helpful advice and kind guidance. The author owes a very important debt to Dr. Akihiro Shimizu for his dedicated support and insightful comments. The author is also thankful to Dr. Aiichiro Nagaki and Dr. Keisuke Asano for their encouragement and meaningful suggestions.

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Yosuke Ashikari

Department of Synthetic Chemistry and Biological Chemistry
Graduate School of Engineering
Kyoto University

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Contents

General Introduction

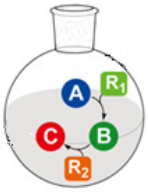
I. Reaction Integration

Organic synthesis has made considerable contribution to the progress of our society by creating and producing a variety of compounds having various biological activities and physical functions. However, the construction of highly designed organic molecules always needs to multi-step reactions, leading time-consuming and costly processes. Therefore, the power and speed of organic synthesis should be enhanced to meet such demands by minimization of synthetic steps with maximization of complexity of molecules. Accordingly, conventional step-by-step synthesis should be supplemented with new synthetic strategy, which combines multiple transformations in a single pot.

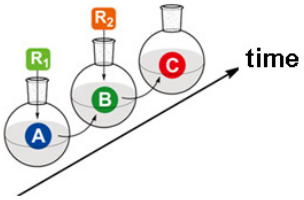
Reaction integration[1] is the concept of combining multiple reactions, where intermediate products are further utilized for subsequent reactions without any purification and isolation. Various types of such transformations have been reported, and because many terminologies have been used, some confusion in this field is caused. Recently Yoshida and co-workers have proposed a new terminology;[2] (a) *time and space integration*,[3] where all reaction components are mixed at once to perform a sequence of reactions simultaneously in a single batch reactor, (b) *time integration*,[4] where reaction components are added at intervals of time to perform a sequence of reactions in a single batch reactor, and (c) *space integration*,[5] where a sequence of reactions is performed in different reactors using a flow system (Scheme 1).

Scheme 1. Classification of Reaction Integration. **A**: Starting Material, **B**: Intermediate, **C**: Product, $\mathbf{R_1}$ and $\mathbf{R_2}$: Reagents.

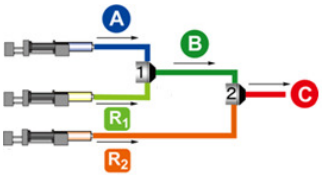
(a) time and space integration



(b) time integration



(c) space integration



The concept of reaction integration is also applicable to unstable reactive intermediates. With a proper integration method, highly unstable reactive species would be swiftly utilized to a subsequent reaction before they decompose. Such integration of reactions, different

from reaction integration using stable intermediates, which is basically possible in a traditional step-by-step synthetic method, would allow a novel transformation which conventional methods will never achieve.

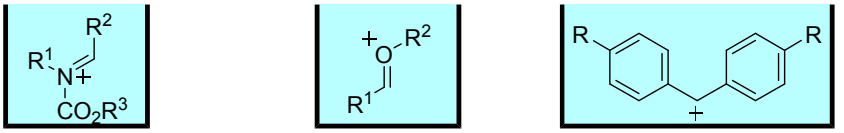
II. Electroorganic Synthesis

Organic electrochemistry provides a powerful means for synthesizing and modifying organic molecules.[6,7] The advantages of this technique lie in its utility for selective oxidation and reduction of functional groups, generation of highly reactive intermediates, and reversing the polarity of functional groups. Because electrochemical processes utilize neutral reaction conditions and are applicable to organic compounds of a wide range of oxidation and reduction potentials, many of these transformations are unique to electrochemistry. Therefore, use of the electrochemical method to complement conventional methods can open new strategies for the synthesis of complex molecules.

Especially, electrochemical oxidation allows irreversible generation of transient cationic species, which play a key role in organic synthesis. Conventionally, carbocations can be generated by "acid-promoted" method, where a proton or a Lewis acid activates a leaving group leading to the heterolysis of the bond between the carbon and the leaving group to generate the carbocation. Because these steps are reversible, several species often exist in the solution as an equilibrium mixture. By contrast, anodically oxidation allows for irreversible generation of carbocations. Furthermore, the oxidation method does not need heteroatomic leaving groups; oxidative cleavage of carbon−carbon, carbon−hydrogen bond gives the corresponding carbocations.[8] Although plenty of electrochemical oxidative reactions have been developed, the organic cations are usually generated in the presence of a nucleophile, which swiftly traps the cations in situ.

Recently, Yoshida and co-workers have developed low-temperature electrochemical oxidation method called the "cation pool" method,[6c] providing a new method in the chemistry of organic cations. In this method, anodic oxidation is carried out at low temperature such as −78 ^{o}C in order to avoid decomposition of the carbocations. The "cation pool" method allows the carbocations, such as *N*-acyliminium ions,[9] alkoxycarbenium ions,[10] and diarylcarbenium ions,[11] to be accumulated in relatively high concentrations in the absence of nucleophiles (Scheme 2). After electrolysis, the organic cation pools are subsequently allowed to react with carbon nucleophiles to form a carbon−carbon bond giving desired products (*time integration*).

Scheme 2. Cation Pools of Carbocations.

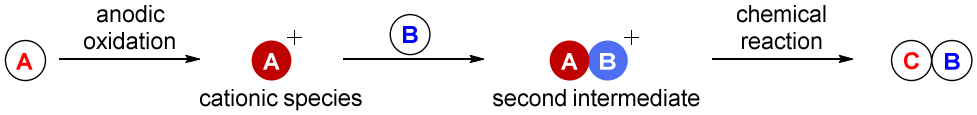


***N*-acyliminium ion pool** **alkoxycarbenium ion pool** **diarylcarbenium ion pool**

III. Reaction Integration Using Electrochemically Generated Cationic Species

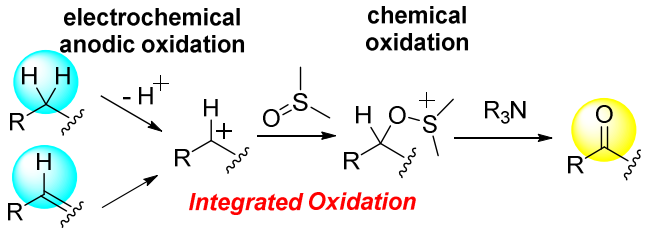
This thesis focuses on the integration of electrochemical oxidation and chemical reactions using electrochemically generated cationic reactive intermediates. Different from the conventional anodic oxidation method, an electrochemically generated cationic intermediate is directly converted to another reactive intermediate which is used in a subsequent chemical reaction. It means that reactive species, which should be swiftly converted to the neutral final product because of their instability, are treated as "starting materials" of sequential reactions. Reaction integration, which provides the way for combining multiple organic reactions by means of reaction intermediates, and electrochemical organic synthesis, which provides the way for irreversible generation of various cationic species, are *integrated*. (Scheme 3).

Scheme 3. Reaction Integration Using Electrochemically Generated Cationic Species.



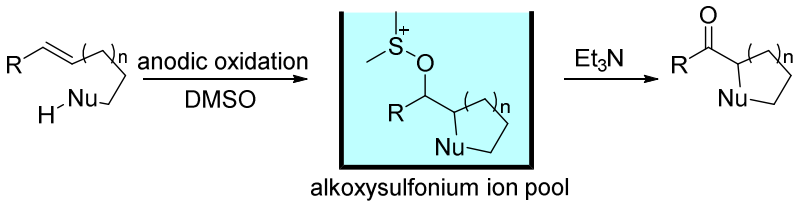
In Chapter 1, the integrated electrochemical−chemical oxidation *via* alkoxysulfonium ions is described (Scheme 4). An electrochemically generated carbocations are reacted with dimethyl sulfoxide (DMSO) to give the corresponding alkoxysulfonium ions, which are well-known as key intermediates of Swern−Moffatt oxidation.[12] The accumulated alkoxysulfonium ions are reacted with triethylamine to give the corresponding carbonyl compound. Thus, the electrochemical oxidation and the chemical oxidation are integrated by the intermediacy of alkoxysulfonium ions, providing a novel four-electron oxidation method. Moreover, reaction integration solves the problem of overoxidation because the conditions of the last step are very mild, and final products are never exposed to the oxidative conditions. This chapter demonstrates an example of the use of electrochemically generated cationic intermediates for a subsequent chemical reaction.

Scheme 4. Integrated Electrochemical−Chemical Oxidation *via* Alkoxysulfonium Ions.



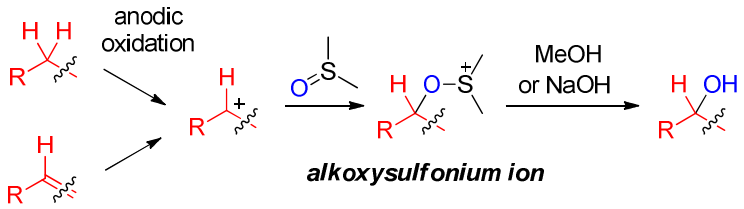
Chapter 2 describes the integration of the electrooxidative cyclization and the chemical oxidation using alkoxysulfonium ion intermediates (Scheme 5). Electrooxidative cyclization[13] is the anodic oxidation of alkenes having a nucleophilic moiety, where one electron oxidation of the olefinic part is attacked by the intramolecular nucleophilic group generating the corresponding cyclized radical cations. Further oxidation followed by the intermolecular attack of the second nucleophile (usually solvent molecule) gives the final products. It was found that the electrooxidative cyclization can be effectively integrated with Swern−Moffatt type chemical oxidation using dimethyl sulfoxide as the second nucleophile. This chapter suggests a potential synthetic utility of the present approach for constructing cyclic molecule backbones.

Scheme 5. Integration of Electrooxidative Cyclization and Chemical Oxidation *via* Alkoxysulfonium Ions.



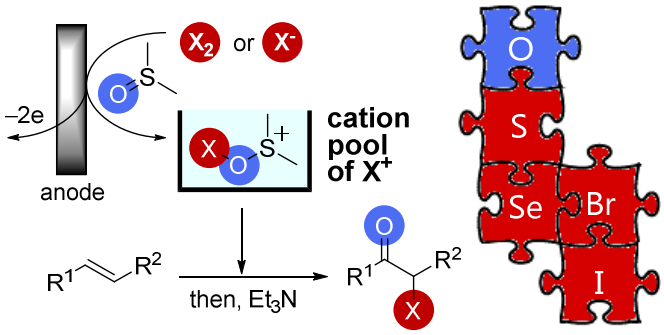
In Chapter 3, the electrochemical oxidative hydroxylation *via* alkoxysulfonium ions is described (Scheme 6). Electrochemically generated alkoxysulfonium ions, which are converted to carbonyl compounds in Chapter 1 and 2, can also be converted to the corresponding alcoholic products by treatment of methanol or aqueous sodium hydroxide. It means that a reagent for the second step changes the oxidation state of the final products; four-electron oxidation or two-electron oxidation. The oxidation of carbon−hydrogen bond and carbon−carbon double bond to carbon−oxygen bond generally needs special methods because the alcoholic products are often more oxidatively active than the starting materials, therefore the overoxidation easily occurs. This present approach allows for the selective synthesis of alcohols and diols by means of alkoxysulfonium ion intermediates.

Scheme 6. Electrochemical Oxidative Hydroxylation Mediated by Alkoxysulfonium Ions.



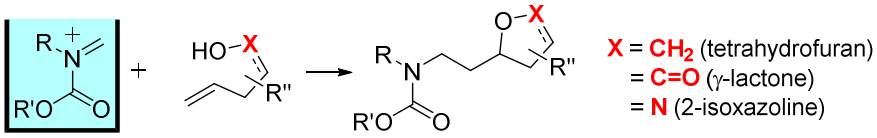
Chapter 4 describes halogen and chalcogen cation pools stabilized by dimethyl sulfoxide, and their synthetic utility for alkene difunctionalization (Scheme 7). It was found that cations of halogens (bromine and iodine) and chalcogens (sulfur and selenium), whose high instabilities make it difficult or impossible to be stored, can be stabilized by dimethyl sulfoxide enabling their accumulation in the solution. The resulting cation pools serve as versatile reagents for alkene difunctionalization; both a halogen or chalcogen atom and dimethyl sulfoxide are introduced to the carbon−carbon double bond. The resulting alkoxysulfonium ions are converted to carbonyl compounds by treatment with triethylamine. In addition, the halogen and chalcogen cation pools reacted with alkenes having a nucleophilic moiety and dienes to give cyclized products.

Scheme 7. Halogen and Chalcogen Cation Pools Stabilized by Dimethyl Sulfoxide, and Their Reactions with Alkenes.



Chapter 5 describes the reactions of *N*-acyliminium ion pools with alkenes having a nucleophilic moiety such as a hydroxyl group, a carboxylic acid moiety, and an oxime moiety to construct a cyclic structure (Scheme 8). *N*-acyliminium ion pools generated from low temperature anodic oxidation reacted with alkenes bearing a hydroxyl group in an appropriate position to give compounds having a tetrahydrofuran ring. The reaction proceeded *via* diastereospecific manner indicating a concerted mechanism, where an intramolecular hydroxyl group participates. *N*-acyliminium ions also reacted with an alkene having a carboxylic acid moiety to generate a lactone ring backbone, and reacted with an alkenyl oxime giving a 2-isoxazoline structure.

Scheme 8. The Reaction of *N*-Acyliminium Ion Pools with Alkenes Having a Nucleophilic Moiety.



References

(1) Reviews: (a) Schmidt, B. *Pure Appl. Chem.* **2006**, *78*, 469. (b) Enders, D.; Hüttl, M. R. M.; Grondal, G.; Raabe, G. *Nature* **2006**, *441*, 861. (c) Yoshida, J.; Saito, K.; Nokami, T.; Nagaki, A. *Synlett* **2011**, 1189.

(2) Suga, S.; Yamada, D. Yoshida, J. *Chem. Lett.* **2010**, *39*, 404.

(3) Selected recent examples: (a) Bigi, M. A.; White, M. C. *J. Am. Chem. Soc.* **2013**, *135*, 7831. (b) Arceo, E.; Jurberg, I. D.; Álvarez-Fernández, A.; Melchiorre, P. *Nat. Chem.* **2013**, *5*, 750. (c) Trenner, J.; Depken, C.; Weber, T.; Breder, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 8952. (d) Michlik, S.; Kempe, R. *Angew. Chem., Int. Ed.* **2013**, *52*, 6326. (d) Geary, L. M.; Glasspoole, B. W.; Kim, M. M.; Krische, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 3796. (e) Tang, Q.; Xia, D.; Jin, X.; Zhang, Q.; Sun, X.-Q.; Wang, C. *J. Am. Chem. Soc.* **2013**, *135*, 4628. (f) Pirnot, M. T.; Rankic, D. A.; Martin, D. B. C.; MacMillan, D. W. C. *Science* **2013**, *339*, 1593. (g) Toh, Q. Y.; McNally, A.; Vera, S.; Erdmann, N.; Gaunt, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 3772. (h) Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc.* **2013**, *135*, 11799. (i) Ohmura, T.; Kijima, A.; Komori, Y.; Suginome, M. *Org. Lett.* **2013**, *15*, 3510. (j) Miura, T.; Tanaka, T.; Biyajima, T.; Yada, A.; Murakami, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 3883. (k) Fukata, Y.; Asano, K.; Matsubara, S. *J. Am. Chem. Soc.* **2013**, *135*, 12160. (l) Pünner, F.; Hilt, G. *Eur. J. Org. Chem.* **2013**, 5580.

(4) Selected recent examples: (a) Yuan, C.; Liang, Y.; Hernandez, T.; Berriochoa, A.; Houk, K. N.; Siegel, D. *Nature* **2013**, *499*, 192. (b) Rahimi, A.; Azarpira, A.; Kim, H.; Ralph, J.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 6415. (c) Morofuji, T.; Shimizu, A.; Yoshida, J. *J. Am. Chem. Soc.* **2013**, *135*, 5000. (d) Matsumoto, K.; Sanada, T.; Shimazaki, H.; Shimada, K.; Hagiwara, S.; Fujie, S.; Ashikari, Y.; Suga, S.; Kashimura, S.; Yoshida, J. *Asian J. Org. Chem.* **2013**, *2*, 325. (e) Minami, Y.; Yoshiyasu, H.; Nakao, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 883.

(5) Selected recent examples: (a) Chen, M.; Buchwald, S. L. *Angew. Chem., Int. Ed.*

2013, *52*, 4247. (b) Nagaki, A.; Ichinari, D.; Yoshida, J. *Chem. Commun.* **2013**, *49*, 3242. (c) Nagaki, A.; Uesugi, Y.; Kim, H.; Yoshida, J. *Chem.−Asian J.* **2013**, *8*, 705. (d) Bourne, S. L.; O'Brien, M.; Kasinathan, S.; Koos, P.; Tolstoy, P.; Hu, D. X.; Bates, R. W.; Martin, B.; Schenkel, B.; Ley, S. V. *ChemCatChem* **2013**, *5*, 159. (e) Nagaki, A.; Yamada, D.; Yamada, S; Doi, M.; Tomida, Y.; Takabayashi, N.; Yoshida, J. *Aust. J. Chem.* **2013**, *66*, 199. (f) Giovine, A.; Musio, B.; Degennaro, L.; Falcicchio, A.; Nagaki, A.; Yoshida, J.; Luisi, R. *Chem.−Eur. J.* **2013**, *19*, 1872.

(6) Reviews: (a) Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527. (b) Sperry, J. B.; Wright, D. L. *Chem. Soc. Rev.* **2006**, *35*, 605. (c) Yoshida, J.; Kataoka, K.; Horcajada, R.; Nagaki, A. *Chem. Rev.* **2008**, *108*, 2265.

(7) Recent examples: (a) Bours, J.; Morton, M.; Fry. A. J. *Tetrahedron Lett.* **2012**, *53*, 1015. (b) Zeng, C.-c.; Zhang, N.-t.; Lam, C. M.; Little, R. D. *Org. Lett.* **2012**, *14*, 1314. (c) Dai, J.-J.; Huang, Y.-B.; Fang, C.; Guo, Q.-X.; Fu, Y. *ChemSusChem* **2012**, *5*, 617. (d) Kirste, A.; Elsler, B.; Schnakenburg, G.; Waldvogel, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 3571. (e) Ishiguro, Y.; Inagi, S.; Fuchigami, T. *J. Am. Chem. Soc.* **2012**, *134*, 4034. (f) Finney, E. E.; Ogawa, K. A.; Boydston, A. J. *J. Am. Chem. Soc.* **2012**, *134*, 12374. (g) Sumi, K.; Saitoh, T.; Natsui, K.; Yamamoto, T.; Atobe, M.; Einaga, Y.; Nishiyama, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 5443. (h) Shida, N.; Ishiguro, Y.; Atobe, M.; Fuchigami, T.; Inagi, S. *ACS Macro Lett.* **2012**, *1*, 656. (i) Yamaguchi, Y.; Okada, Y.; Chiba, K. *J. Org. Chem.* **2013**, *78*, 2826.

(8) Electrochemical oxidative cleavage of carbon−silicon bond (electroauxiliary): (a) Yoshida, J.; Maekawa, T.; Murata, T.; Matsunaga, S.; Isoe, S. *J. Am. Chem. Soc.* **1990**, *112*, 1962. (b) Yoshida, J.; Nishiwaki, K. *J. Chem. Soc., Dalton Trans.* **1998**, 2589. The sulfur electroauxiliaries, see: (c) Yoshida, J.; Sugawara, M.; Kise, N. *Tetrahedron Lett.* **1996**, *37*, 3157. (d) Yoshida, J.; Sugawara, M.; Tatsumi, M.; Kise, N. *J. Org. Chem.* **1998**, *63*, 5950. (e) Chiba, K.; Uchiyama, R.; Kim, S.; Kitano, Y.; Tada, M. *Org. Lett.* **2001**, *3*, 1245.

(9) Selected examples: (a) Yoshida, J.; Suga, S.; Suzuki, S.; Kinomura, N.; Yamamoto, A.; Fujiwara, K. *J. Am. Chem. Soc.* **1999**. *121*, 9546. (b) Suga, S.; Suzuki, S.; Yoshida, J. *J. Am. Chem. Soc.* **2002**, *124*, 30. (c) Yoshida, J.; Suga, S. *Chem.−Eur. J.* **2002**, *8*, 2650. (d) Suga, S.; Watanabe, M.; Yoshida, J. *J. Am. Chem. Soc.* **2002**, *124*, 14824. (e) Suga, S.; Nagaki, A.; Tsutsui, Y.; Yoshida, J. *Org. Lett.* **2003**, *5*, 945. (f) Suga, S.; Suzuki, S.; Maruyama, T.; Yoshida, J. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1545. (g) Suga, S.; Kageyama, Y.; Babu, G.; Itami, K.; Yoshida, J. *Org. Lett.* **2004**, *6*, 2709. (h) Suga, S.; Nishida, T.; Yamada, D.; Nagaki, A.; Yoshida, J. *J. Am. Chem. Soc.* **2004**, *126*, 14338. (i) Nagaki, A.; Kawamura, K.; Suga, S.; Ando, T.; Sawamoto, M.; Yoshida, J. *J. Am. Chem. Soc.* **2004**, *126*, 14702. (j) Suga, S.; Tsutsui, Y.; Nagaki, A.;

Yoshida, J. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 1206. (k) Maruyama, T.; Suga, S.; Yoshida, J. *J. Am. Chem. Soc.* **2005**, *127*, 7324. (l) Nagaki, A.; Togai, M.; Suga, S.; Aoki, N.; Mae, K. Yoshida, J. *J. Am. Chem. Soc.* **2005**, *127*, 11666. (m) Maruyama, T.; Suga, S.; Yoshida, J. *Tetrahedron* **2006**, *62*, 6519. (n) Suga, S.; Watanabe, M.; Song, C.-H.; Yoshida, J. *Electrochemistry* **2006**, *74*, 672. (o) Maruyama, T.; Mizuno, Y.; Shimizu, I.; Suga, S.; Yoshida, J. *J. Am. Chem. Soc.* **2007**, *129*, 1902. (p) Suga, S.; Shimizu, I.; Ashikari, Y.; Mizuno, Y.; Maruyama, T.; Yoshida, J. *Chem. Lett.* **2008**, *37*, 1008.

(10) Selected examples: (a) Suga, S.; Suzuki, S.; Yamamoto, A.; Yoshida, J. *J. Am. Chem. Soc.* **2000**, *122*, 10244. (b) Suzuki, S.; Matsumoto, K.; Kawamura, K.; Suga, S.; Yoshida, J. *Org. Lett.* **2004**, *6*, 3755. (c) Suga, S.; Suzuki, S.; Yoshida, J. *Org. Lett.* **2005**, *6*, 4717. (d) Okajima, M.; Suga, S.; Itami, K.; Yoshida, J. *J. Am. Chem. Soc.* **2005**, *127*, 6930. (e) Suga, S.; Matsumoto, K.; Ueoka, K.; Yoshida, J. *J. Am. Chem. Soc.* **2006**, *128*, 7710. (f) Matsumoto, K.; Ueoka, K.; Suzuki, S.; Suga, S.; Yoshida, J. *Tetrahedron* **2009**, *65*, 10901.

(11) Selected examples: (a) Okajima, M.; Soga, K.; Nokami, T.; Suga, S.; Yoshida, J. *Org. Lett.* **2006**, *8*, 5005. (b) Nokami, T.; Ohata, K.; Inoue, M.; Tsuyama, H.; Shibuya, A.; Soga, K.; Okajima, M.; Suga, S.; Yoshida, J. *J. Am. Chem. Soc.* **2008**, *130*, 10864. (c) Okajima, M.; Soga, K.; Watanabe, T.; Terao, K.; Nokami, T.; Suga, S.; Yoshida, J. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 594. (d) Terao, K.; Watanabe, T.; Suehiro, T.; Nokami, T.; Yoshida, J. *Tetrahedron Lett.* **2010**, *51*, 4107. (e) Nokami, T.; Watanabe, T.; Musya, N.; Morofuji, T.; Tahara, K.; Tobe, Y.; Yoshida, J. *Chem. Commun.* **2011**, *47*, 5575. (f) Nokami, T.; Watanabe, T.; Musya, N.; Suehiro, T.; Morofuji, T.; Yoshida, J. *Tetrahedron* **2011**, *67*, 4664. (g) Nokami, T.; Watanabe, T.; Terao, K.; Soga, K.; Ohata, K.; Yoshida, J. *Electrochemistry* **2013**, *81*, 399.

(12) (a) Kornblum, N.; Powers, J. W.; Anderson, G. J.; Jones, W. J.; Larson, H. O.; Levand, O.; Weaver, W. M. *J. Am. Chem. Soc.* **1957**, *79*, 6562. (b) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165. (c) Phan, T. B.; Nolte, C.; Kobayashi, S.; Ofial, A. R.; Mayr, H. *J. Am. Chem. Soc.* **2009**, *131*, 11392.

(13) (a) New, D. G.; Tesfai, Z.; Moeller, K. D. *J. Org. Chem.* **1996**, *61*, 1578. (b) Xu, H.-C.; Moeller, K. D. *J. Am. Chem. Soc.* **2008**, *130*, 13542. (c) Xu, H.-C.; Moeller, K. D. *J. Am. Chem. Soc.* **2010**, *132*, 2839.

Chapter 1

Integrated Electrochemical−Chemical Oxidation *via* Alkoxysulfonium Ions

Abstract

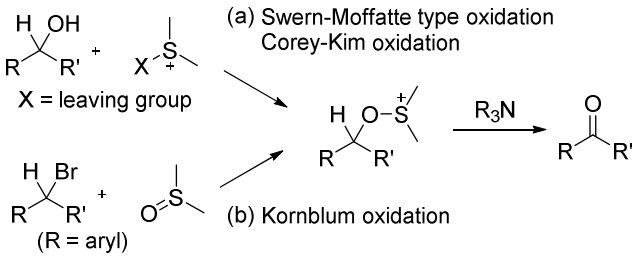
Generation of carbocations by the "cation pool" method followed by the reaction with dimethyl sulfoxide (DMSO) gave the corresponding alkoxysulfonium ions. Alkoxysulfonium ions could also be generated by in situ DMSO trapping of electrochemically generated carbocations. The resulting alkoxysulfonium ions were transformed into carbonyl compounds by treatment with triethylamine. The present integrated electrochemical−chemical oxidation can be applied to the oxidation of diarylmethanes to diaryl ketones, toluenes to benzaldehydes, and aryl-substituted alkenes to 1,2-diketones.

Introduction

Organic synthesis has been developed mainly based on step-by-step synthesis. However, combining multiple steps without isolating intermediates is strongly needed to enhance the power and efficiency of organic synthesis.[1, 2] To this end, chemists have been interested in integration of chemical reactions[3] to develop synthetic transformations that would be otherwise impossible.

Among a variety of reactions used in organic synthesis, selective oxidation of organic compounds still remains as a major challenge.[4] Integration of electrochemical oxidation[5,6] and chemical oxidation would be a nice approach to this challenge, and this chapter deals with an example of such integration that is mediated by an unstable alkoxysulfonium ions as key intermediates. Because treatment of alkoxysulfonium ions with a base such as triethylamine eventually gives the corresponding carbonyl compounds, the present method serves as one of the mildest method for oxidation of organic compounds (DMSO oxidation) (Scheme 1).[7,8] Although alkoxysulfonium ions could be generated by several chemical methods, the oxidation state of the precursors (RR'CH−X, X: heteroatom) and the resulting alkoxysulfonium ions (RR'CH−OS^+Me_2) are the same, and the overall reaction to give RR'C=O is two-electron oxidation. If substrates of lower oxidation state, for example $RR'CH_2$, could be used to generate alkoxysulfonium ions, the overall reaction would be four-electron oxidation and the method serves as highly useful way of oxidizing organic compounds.

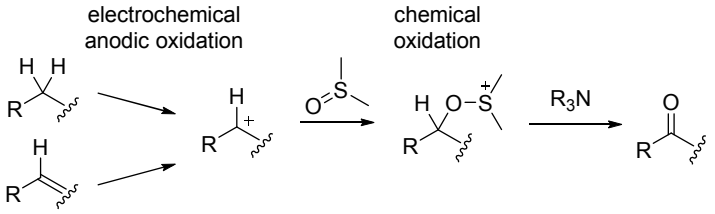
Scheme 1. Chemical Oxidation Mediated by Alkoxysulfonium Ions.



It is well known that electrochemical oxidation serves as a powerful method for generating carbocations and onium ions under mild conditions.[4] In fact, various types of electrochemical oxidation reactions proceed by a mechanism involving carbocations, though carbocations are usually trapped spontaneously by nucleophiles that are present in the reaction media. However, an effective method for generating and accumulating carbocations or onium ions using low temperature electrochemical oxidation has been developed. The method, which is called the "cation pool" method, has been successfully applied to *N*-acyliminium ions,[9] alkoxycarbenium ions,[10] and diarylcarbenium ions.[11] Based on these backgrounds, it seems to be reasonable to consider that the carbocations generated by the "cation pool method" could be used for a

subsequent reaction with DMSO to generate alkoxysulfonium ions, which react with an amine base to give the corresponding carbonyl compounds (Scheme 2). In fact, Mayr and coworkers observed in their mechanistic studies that a diarylcarbenium ions generated by chemical S_N1 reaction reacted with DMSO and that subsequent treatment with triethylamine gave the diaryl ketones.[12] It should be noted that, unlike the chemical methods, the oxidation state of a precursor of the electrochemical method is lower than that of the resulting alkoxysulfonium ion.

Scheme 2. Integrated Electrochemical–Chemical Oxidation Mediated by Alkoxysulfonium Ions.



Results and Discussions

To test the feasibility of the present concept, the reaction of an electrochemically generated diarylcarbenium ion with DMSO was examined (Method A). Thus, diarylcarbenium ion **2a** was generated and accumulated by the electrochemical oxidation of diarylmethane **1a** in CD_2Cl_2 using Bu_4NBF_4 as a supporting electrolyte at −78 °C according to the "cation pool" method (Figure 1).[11] The addition of DMSO to **2a** gave alkoxysulfonium ion **3a**, which was well characterized by NMR analysis at −78 °C. Treatment of the solution of **3a** with triethylamine gave the corresponding diaryl ketone **4a** in 91% yield. This proof-of-principle experiment revealed that the electrochemical reaction and the chemical reaction could be integrated effectively by the intermediacy of a carbocation and an alkoxysulfonium ion. The method is also applicable to diarylmethane **1b** to produce the corresponding diaryl ketone **4b** (Table 1).

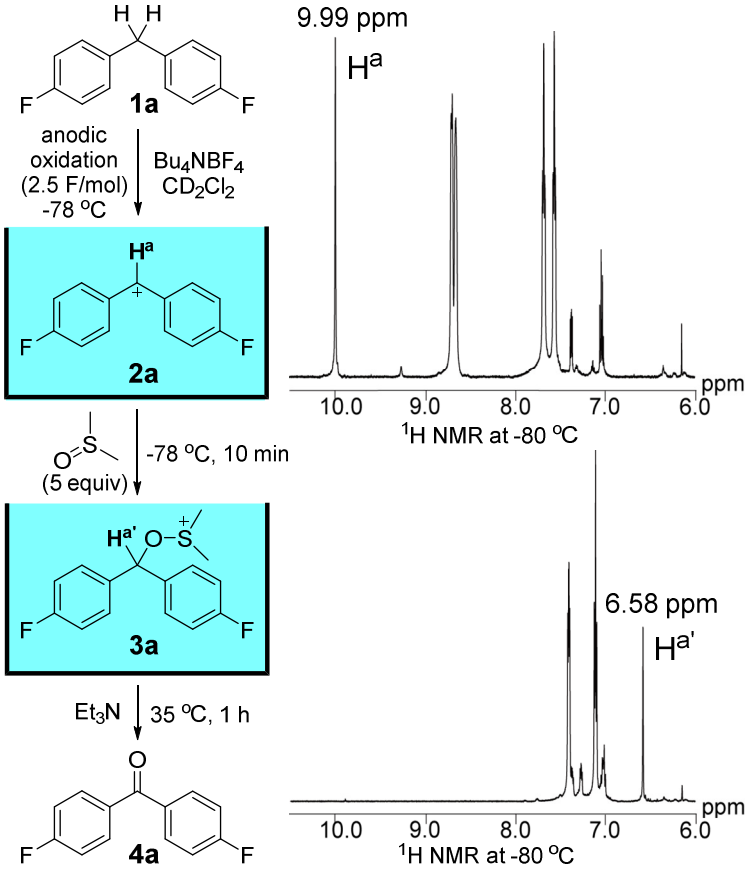


Figure 1. Typical example of integrated electrochemical−chemical oxidation and ^{1}H NMR spectra of the cationic intermediates **2a** and **3a**. Trapping of a "cation pool" with DMSO (Method A).

In-situ trapping of carbocations by DMSO is also effective when the substrate oxidation potential is lower than that of DMSO (1.76 V vs SCE). For example, the electrochemical oxidation of 4-methoxytoluene (**1c**) (1.38 V vs SCE) in 1:2 DMSO-d_6/CD_2Cl_2 (Figure 2, method B) gave alkoxysulfonium ion **3c**, which was characterized by NMR analysis. In this case, the electrolysis could be carried out at 24 °C because the alkoxysulfoniuim ion is more stable than the corresponding carbocation. Treatment of **3c** with triethylamine gave aldehyde **4c** in 86% yield. It is noteworthy that the cation pool method cannot be used in this case because 4-methoxybenzyl cation (**2c**) is not stable enough to accumulate in the solution even at −78 °C. It is also noteworthy that the success of the in situ method is attributed to the fact that **1c** is more easily oxidized than DMSO. In contrast, the oxidation potential of diarylmethane **1a** (1.96 V vs SCE) is higher than that of DMSO, and therefore, the electrochemical oxidation of **1a** should be carried out in the absence of DMSO. However, a wide range of organic compounds can serve as substrates for the in situ method. For example, xanthene (**1d**) was oxidized effectively by method B to give 9-xanthenone (**4d**) (Table1).

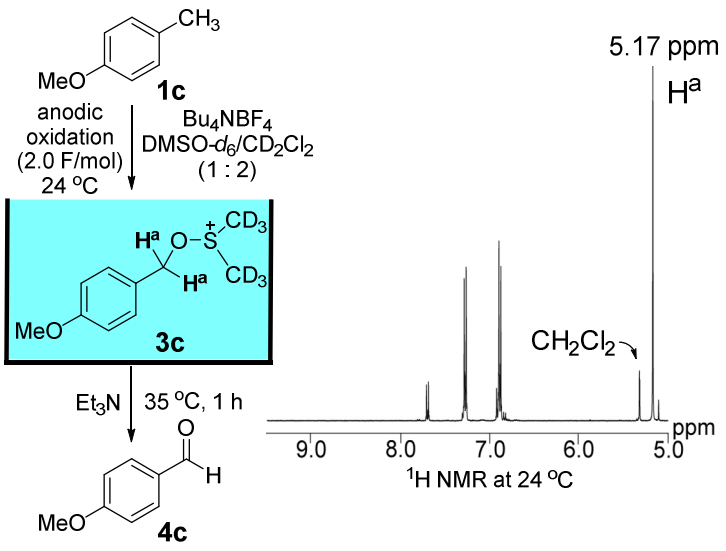
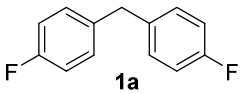
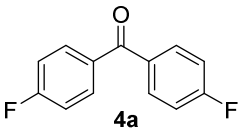
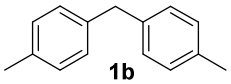
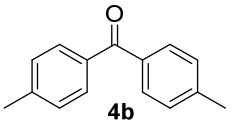
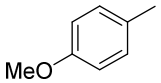
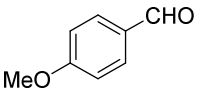
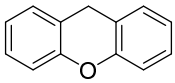
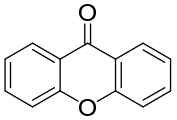


Figure 2. Typical example of integrated electrochemical−chemical oxidation and ^{1}H NMR spectrum of the cationic intermediate **3c**. Trapping of a carbocation with DMSO in-situ (Method B).

Table 1. Integrated Electrochemical−Chemical Oxidation of Organic Compounds[a].

substrate	oxidation potential (V)[b]	method	electricity (F/mol)	product	yield (%)[c]
 **1a**	1.96	A	2.5	 **4a**	91
 **1b**	1.75	A	2.5	 **4b**	62
 **1c**	1.38	B	2.5	 **4c**	86[d]
 **1d**	1.36	B	4.0	 **4d**	84

[a]The reactions were carried out on a 0.25 mmol scale. Method A was according to Figure 1, and Method B was according to Figure 2. [b]Determined by rotating disk electrode (RDE) voltammetry in 0.1 M $LiClO_4/CH_3CN$ using SCE as a reference electrode. [c]Isolated yields after flash chromatography. [d]GC yield.

The present method could be extended to the oxidation of aryl-substituted alkenes. For example, 4,4'-dichloro-*trans*-stilbene (**5a**) was electrochemically oxidized in the presence of

DMSO-d_6 at 0 °C (Figure 3). The NMR study indicated the formation of bisalkoxysulfonium ion **6a** in the solution. Treatment of **6a** with triethylamine gave the corresponding 1,2-diketone **7a** in 83% yield. In contrast, chemical oxidation of *trans*-stilbene using $RuCl_3/NaIO_4$ gives the corresponding 1,2-diketone (benzil) in only 5% yield and the carbon−carbon bond cleavage product (benzoic acid) as the major product.[13] In addition, the conventional electrochemical method also often suffers from overoxidation. For example, anodic oxidation of alkenes,[14] 1,2-diols,[15] and their derivatives often leads to carbon−carbon bond cleavage. The present approach solves this otherwise formidable problem by integration with an extremely mild chemical method such as DMSO oxidation. Therefore, the present method serves as a powerful and highly selective method for the conversion of alkenes **5a**−**e** to 1,2-dicarbonyl compounds **7a**−**e** (Table 2).

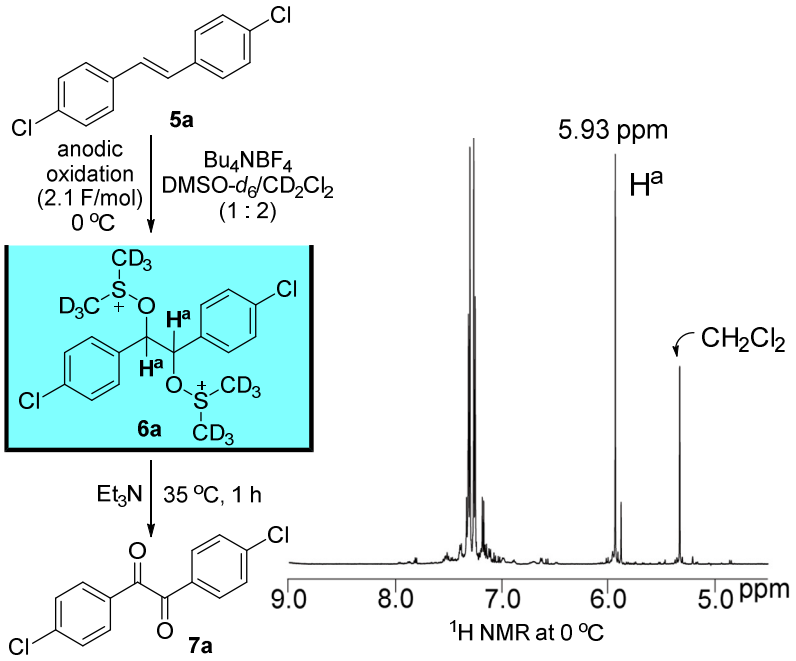
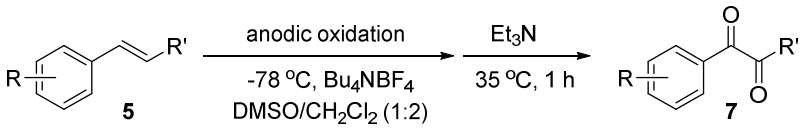
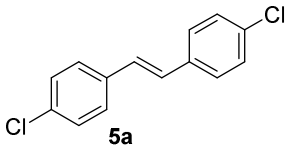
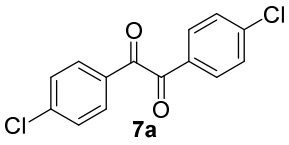
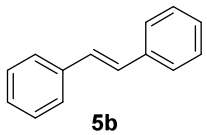
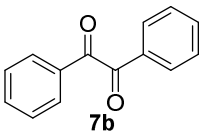
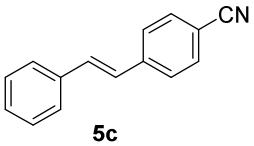
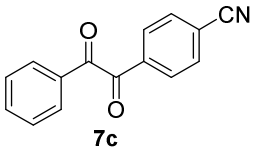
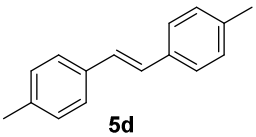
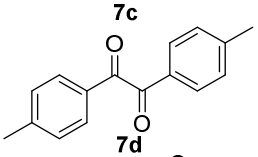
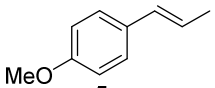
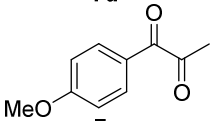


Figure 3. Integrated electrochemical−chemical oxidation of 4,4'-dichloro-*trans*-stilbene (**1e**) and a ^{1}H NMR spectrum of the cationic intermediate **6a**.

Table 2. Integrated Electrochemical−Chemical Oxidation of Alkenes[a].



alkene **5**	oxidation potential (V)[b]	electricity (F/mol)	product **7**	yield (%)[c]
 **5a**	1.36	2.1	 **7a**	83
 **5b**	1.31	2.1	 **7b**	70 (71)[d]
 **5c**	1.44	2.1	 **7c**	50 (74)[e]
 **5d**	1.20	2.1	 **7d**	71
 **5e**	1.09	2.5	 **7e**	55

[a]The reactions were carried out on a 0.25 mmol scale according to Method B shown in Figure 2. [b]Determined by rotating disk electrode (RDE) voltammetry in 0.1 M $LiClO_4/CH_3CN$ using SCE as a reference electrode. [c]Isolated yields after flash chromatography. [d]The reaction was carried out on a 1.3 mmol scale. [e]NMR yield.

Conclusion

The integration of an electrochemical oxidation with a chemical oxidation was achieved by the mediacy of alkoxysulfonium ions, which are key intermediates of DMSO oxidation. An anodic oxidation step and a product-obtaining step were separated by means of *time integration*, preventing the products from being overoxidized. The electrochemical method is often cited as being environmentally favorable because it enables straightforward transformations under mild conditions without the use of hazardous strong chemical reagents.[16] The present method based on integration of the electrochemical method with an extremely mild, environmentally benign chemical method opens a new aspect of the chemistry of oxidation reactions.

Experimental Section

General Remarks. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Varian MERCURY plus-400 (^{1}H 400 MHz, ^{13}C 100 MHz), or JEOL ECA-600P spectrometer (^{1}H 600 MHz, ^{13}C 150 MHz). Chemical shifts are recorded using methin signal of $CHCl_3$ (7.26 ppm for 1H NMR and 77.0 ppm for ^{13}C NMR) 1,1,2,2-Tetrachloroethane (TCE) was used as an internal standard for NMR yield (^{1}H NMR, 5.95 ppm, 2 H). Mass spectra were obtained on JEOL EXACTIVE, and on JEOL JMS SX-102A mass spectrometer. IR spectra were measured with a Shimadzu IRAffinity (FTIR). Merck precoated silica gel F_{254} plates (thickness 0.25 mm) was used for thin-layer chromatography (TLC) analysis. Flash chromatography was carried out on a silica gel (Kanto Chem. Co., Silica Gel N, spherical, neutral, 40–100 mm). Preparative gel permeation chromatography (GPC) was carried out on Japan Analytical Industry LC-918 equipped with JAIGEL-1H and 2H using $CHCl_3$ as an eluent. Rotating-disk electrode (RDE) voltammetry was carried out using BAS 600C and BAS RRDE-3 rotating disk electrodes. Measurements were carried out in 0.1 M $LiClO_4/CH_3CN$ using a glassy carbon disk working electrode, a platinum wire counter electrode, and an SCE reference electrode with sweep rate of 10 mV/s at 3000 rpm. All reactions were carried out under argon atmosphere unless otherwise noted. The anodic oxidation was carried out using an H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon JF-20-P7, ca. 160 mg, dried at 300 ^{o}C/1 mmHg for 4 hours before use) and a platinum plate cathode (10 mm x 10 mm).

Materials. Bu_4NBF_4 was purchased from TCI and dried at 50 ^{o}C/1 mmHg overnight. $Bu_4NB(C_6F_5)_4$ was prepared according to the reported procedure.[17] Dichloromethane was washed with water, distilled from P_2O_5, redistilled from dried K_2CO_3 to remove a trace amount of acid, and stored over molecular sieves 4A. Triethylamine (Et_3N) was refluxed with calcium hydride, distilled, and stored over molecular sieves 4A. CD_2Cl_2 was dried over molecular sieves 4A before use. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification.

The approach based on the "cation pool" method (Method A). In the anodic chamber were placed bis(4-fluorophenyl)methane (**1a**) (49.6 mg, 0.243 mmol) and 0.3 M Bu_4NBF_4/CH_2Cl_2 (10 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (60 μL, 0.68 mmol) and 0.3 M Bu_4NBF_4/CH_2Cl_2 (10 mL). The constant current electrolysis (8.0 mA) was carried out at −78 ^{o}C with magnetic stirring until 2.5 F/mol of electricity was consumed. Then mixture of DMSO (90 μL 1.27 mmol) and 0.3 M Bu_4NBF_4/CH_2Cl_2 (180 μL) was added to the anodic chamber at −78 ^{o}C and the mixture was stirred for 5 min. Then triethylamine (1.0 mL) was added to both the anodic and the cathodic chambers, and the resulting mixture was heated at 35 ^{o}C and stirred for additional 1 hour. The solutions in the anodic and cathodic chambers were poured into

water (20 mL). The mixture was extracted with CH_2Cl_2 (20 mL x 3), and was dried over Na_2SO_4. After removal of solvent under reduced pressure, the residue was quickly filtered through a short column (2 x 4 cm) of silica gel to remove Bu_4NBF_4 by using hexane/EtOAc 1:1 with 1 vol% of triethylamine as an eluent. After removal of the solvent under reduced pressure the crude product was purified by flash chromatography (hexane/EtOAc 12:1) to obtain **4,4'-difluorobenzophenone** (**4a**) in 91% yield (48.5 mg, 0.222 mmol). TLC R_f 0.48 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (m, 4 H), 7.82 (m, 4 H). The spectra were in agreement with the literature.[18]

Low temperature NMR analyses of carbocation 2a and alkoxysulfonium ion 3a. In the anodic chamber were placed a solution of diarylmethane **1a** (25.5 mg, 0.125 mmol) in 0.1 M Bu_4NBF_4/CD_2Cl_2 (5.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (11 μL) and 0.1 M Bu_4NBF_4/CD_2Cl_2 (5.0 mL). The constant current electrolysis (4.0 mA) was carried out at −78 °C with magnetic stirring until 2.5 F/mol of electricity was consumed. The reaction mixture in the anodic chamber (0.6 mL) was transferred to a 5 mm ϕ NMR tube with septum cap under argon atmosphere at −78 °C. Chemical shifts are reported using methylene signals of CH_2Cl_2 at δ 5.32 as an internal standard. Selected signals for **2a** (3.5−10.0 ppm for ^{1}H NMR at −80 °C). ^{1}H NMR (600 MHz, CD_2Cl_2) δ 9.99 (s, 1 H), 8.65−8.70 (m, 4 H), 7.54−7.70 (m, 4 H). The spectrum was in agreement with the literature.[11c]

To the solution of **2a** in a 5 mm ϕ NMR tube DMSO (10 μL) diluted with CD_2Cl_2 (20 μL) was added at −78 °C. After quickly shaking of the reaction mixture, NMR analysis was immediately started. Chemical shifts are reported using methylene signals of CH_2Cl_2 at δ 5.32 as an internal standard. Selected signals for **3a** (3.5−10.0 ppm for ^{1}H NMR at −80 °C, 60.0−200.0 ppm for ^{13}C NMR at −80 °C). ^{1}H NMR (600 MHz, CD_2Cl_2) δ 6.58 (s, 1 H), 7.10−7.13 (m, 4 H), 7.40−7.42 (m, 4 H): ^{13}C NMR (150 MHz, CD_2Cl_2) δ 87.6, 115.7 and 115.8, 129.7 and 129.7, 161.7.

4,4'-Dimethylbenzophenone (4b). Electrochemical oxidation (2.5 F/mol) of di-4-tolylmethane (**1b**) (47.9 mg, 0.244 mmol) and subsequent treatment with DMSO and Et_3N followed by flash chromatography (hexane/EtOAc 12:1) gave the title compound (31.8 mg, 62%); TLC R_f 0.48 (hexane/EtOAc 5:1):^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 6 H), 7.19 (d, J = 8.0 Hz, 4 H), 7.59 (d, J = 8.0 Hz, 4 H). The spectra were in agreement with the literature.[23]

The approach based on in-situ trapping of carbocations with DMSO (Method B). In the anodic chamber were placed 4-methoxytoluene (**1c**) (29.9 mg, 0.245 mmol), Bu_4NBF_4 (350 mg, 1.06 mmol), DMSO (3.6 mL), and 0.3 M Bu_4NBF_4/CH_2Cl_2 (6.4 mL). In the cathodic chamber were placed trifluoromethane- sulfonic acid (55 μL, 0.62 mmol) and 0.3 M Bu_4NBF_4/CH_2Cl_2 (10 mL). The constant current electrolysis (16.0 mA) was carried out at 24 °C with magnetic stirring

until 2.5 F/mol of electricity was consumed. Then the anodic solution was quantitatively transferred to a 50 mL round-bottom flask under argon atmosphere, and triethylamine (1.0 mL) was added. The resulting mixture was heated at 35 ^{o}C and stirred for additional 1 hour. The solution was poured into water (20 mL), and the mixture was extracted with CH_2Cl_2 (20 mL x 3). The extracts were dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was quickly filtered through a short column (2 x 4 cm) of silica gel to remove Bu_4NBF_4 by using Et_2O as an eluent. The GC analysis using hexadecane as an internal standard indicated that 4-anisaldehyde (**4c**) was obtained in 86% yield (0.212 mmol). TLC R_f 0.26 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 1 H), 7.00 (d, J = 8.8 Hz, 2 H), 7.84 (d, J = 8.8 Hz, 2 H), 9.89 (s, 1 H). The spectra were in agreement with the literature.[18]

NMR analysis of alkoxysulfonium ion 3c. In the anodic chamber were placed 4-methoxytoluene (**1c**) (15.0 mg, 0.123 mmol), Bu_4NBF_4 (150 mg), DMSO-d_6 (1.7 mL), and CD_2Cl_2 (3.3 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (19.7 μL), Bu_4NBF_4 (150 mg), DMSO-d_6 (1.7 mL), and CD_2Cl_2 (3.3 mL). The constant current electrolysis (4.0 mA) was carried out at 24 ^{o}C with magnetic stirring until 2.5 F/mol of electricity was consumed. The reaction mixture of the anodic chamber (0.6 mL) was transferred to a 5 mm ϕ NMR tube with septum cap under argon atmosphere at room temperature. Chemical shifts are reported using methylene signals of CH_2Cl_2 at δ 5.32 as an internal standard. Selected signals for **3c** (3.5−10.0 ppm for ^{1}H NMR at 24 ^{o}C, 60−200.0 ppm for ^{13}C NMR at 24 ^{o}C). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 3.68 (s, 3 H), 5.17 (s, 2 H), 6.88 (d, J = 8.8 Hz, 2 H), 7.27 (d, J = 8.8 Hz, 2 H); ^{13}C NMR (150 MHz, CD_2Cl_2) δ 55.3, 57.3, 114.4, 114.9, 133.1, 161.3.

9-Xanthenone (4d). Electrochemical oxidation (8 mA, 4.0 F/mol) of xanthene (**1d**) (46.6 mg, 0.255 mmol) and subsequent treatment with Et_3N in one-pot followed by flash chromatography (hexane/EtOAc) gave the title compound (40.4 mg, 84%); TLC R_f 0.31 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (tt, J = 0.8, 8.0 Hz, 2 H), 7.49 (d, J = 9.2 Hz, 2 H), 7.73 (dt, J = 1.6, 8.4 Hz, 2 H), 8.34 (dd, J = 1.6, 8.0 Hz, 2 H). The spectra were in agreement with the literature.[23]

Oxidation of 4,4'-dichloro-*trans*-stilbene (5a) (Typical Procedure for Oxidation of Alkenes to 1,2-Diketones). In the anodic chamber were placed 4,4'-dichloro-*trans*-stilbene (**5a**) (64.1 mg, 0.257 mmol), Bu_4NBF_4 (350 mg, 1.06 mmol), DMSO (3.6 mL) and 0.3 M Bu_4NBF_4/CH_2Cl_2 (6.4 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (60 μL, 0.68 mmol) and 0.3 M Bu_4NBF_4/CH_2Cl_2 (10 mL). The constant current electrolysis (8.0 mA) was carried out at 0 ^{o}C with magnetic stirring until TLC analysis indicated that **5a** was consumed (2.1 F/mol of electricity). Then 1 mL of Et_3N was added to both the anodic and the

cathodic chambers, and the resulting mixture was heated at 35 °C with stirring for 1 hour. The anodic and cathodic solutions were poured into water (20 mL), and the mixture was extracted with CH_2Cl_2 (20 mL x 3). The extracts were dried over Na_2SO_4. After removal of solvent under reduced pressure, the crude product was purified by flash chromatography (CH_2Cl_2 with 1 vol% of Et_3N) gave **4,4'-dichlorobenzil** (**7a**) (59.7 mg, 83%); TLC R_f 0.60 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.0 Hz, 4 H), 7.77 (d, *J* = 8.0 Hz, 4 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 129.5, 131.1, 131.3, 141.8, 192.3; IR ($CHCl_3$) 1678.7, 3019.7 cm^{-1}; LRMS (EI) *m/z* 278 [M^+], 139 [$(M-ClC_6H_4CO)^+$]; HRMS (EI) calcd for $C_{14}H_8O_2Cl_2$ [M^+]: 277.9901, found: 277.9896.

Low temperature NMR analysis of alkoxysulfonium ion 6a. In the anodic chamber were placed 4,4'-dichloro-*trans*-stilbene (**5a**) (30.7 mg, 0.124 mmol), Bu_4NBF_4 (160 mg, 0.486 mmol), DMSO-d_6, (1.7 mL) and CD_2Cl_2 (3.3 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (22 μL, 0.25 mmol) and 0.1 M Bu_4NBF_4/CD_2Cl_2 (5.0 mL). The constant current electrolysis (4.0 mA) was carried out at 0 °C with magnetic stirring until 2.1 F/mol of electricity was consumed. The reaction mixture of the anodic chamber (0.6 mL) was transferred to a 5 mm ϕ NMR tube with septum cap under argon atmosphere at room temperature. Chemical shifts are reported using methylene signals of CH_2Cl_2 at δ 5.32 as an internal standard. Selected signals for **6a** (3.5−10.0 ppm for ^{1}H NMR at 0 °C, 60.0−200.0 ppm for ^{13}C NMR at 0 °C). ^{1}H NMR (600 MHz, CD_2Cl_2) δ 5.93 (s, 2 H), 7.25 (d, *J* = 8.4 Hz, 4 H), 7.29 (d, *J* = 8.4 Hz, 4 H); ^{13}C NMR (150 MHz, CD_2Cl_2) δ 87.7, 129.7, 130.3, 130.9, 136.6.

Benzil (7b). Electrochemical oxidation (2.1 F/mol) of *trans*-stilbene (**5b**) (44.8 mg, 0.249 mmol), subsequent treatment with Et_3N followed by flash chromatography (hexane/EtOAc 7:1 with 1 vol% of Et_3N) gave the title compound (36.8 mg, 70%); TLC R_f 0.27 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (t, *J* = 8.0 Hz, 4 H), 7.66, (t, *J* = 7.6 Hz, 2 H), 7.98 (d, *J* = 8.0 Hz, 4 H). The spectra were in agreement with the literature.[19]

4-Cyanobenzil (7c). Electrochemical oxidation (2.1 F/mol) of 4-cyano-*trans*-stilbene (**5c**) (commercially available, TCI) (52.4 mg, 0.255 mmol) and subsequent treatment with Et_3N in one-pot afforded the crude product (74% NMR yield). The title compound was obtained by flash chromatography (CH_2Cl_2 with 3 vol% of Et_3N) and GPC (29.7 mg, 50%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (t, *J* = 7.2 Hz, 2 H), 7.71 (t, *J* = 7.6 Hz, 1 H), 7.82 (d, *J* = 8.8 Hz, 2 H), 7.98 (d, *J* = 7.6 Hz, 2 H), 8.09 (dd, *J* = 0.4, 8.0 Hz, 2 H). The spectra were in agreement with the literature.[19]

4,4'-Dimethylbenzil (7d). Electrochemical oxidation (2.1 F/mol) of 4,4'-dimethyl-*trans*-stilbene (**5d**) (49.7 mg, 0.239 mmol) and subsequent treatment with Et_3N followed by flash

chromatography (hexane/EtOAc 7:1 with 1 vol% of Et_3N) gave the title compound (40.7 mg, 71%); TLC R_f 0.30 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 6 H), 7.30 (d, J = 8.0 Hz, 4 H), 7.86 (d, J = 7.6 Hz, 4 H). The spectra were in agreement with the literature.[18]

1-(4-Anysil)propan-1,2-dione (7e). Electrochemical oxidation (2.5 F/mol) of *trans*-anethole (**5e**) (38.5 mg, 0.260 mmol) and subsequent treatment with Et_3N followed by flash chromatography (hexane/EtOAc 10:1 with 1 vol% of Et_3N) gave the title compound (25.4 mg, 55%); TLC R_f 0.26 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (s, 3 H), 3.88 (s, 3 H), 6.96 (d, J = 7.6 Hz, 2 H), 8.01 (d, J = 8.0 Hz, 2 H). The spectra were in agreement with the literature.[20]

References

(1) For reviews: (a) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312. (b) Ugi, I. *Pure Appl. Chem.* **2001**, *73*, 187. (c) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365. (c) de Meijere, A.; von Zezschwitz, P.; Bräse, S. *Acc. Chem. Res.* **2005**, *38*, 413. (d) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (e) Schmidt, B. *Pure Appl. Chem.* **2006**, *78*, 469. (f) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861.

(2) For recent examples: (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (b) Bienaymé, H.; Hulme, C.; Oddon, O.; Schmitt, P. *Chem.−Eur. J.* **2000**, *6*, 3321. (c) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101. (d) Ajamian, A.; Gleason, J. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 3754. (e) Shimizu, M.; Shimono, K.; Hiyama, T. *Chem. Lett.* **2006**, *35*, 838. (f) Clarke, P. A.; Santos, S.; Martin, W. H. C. *Green Chem.* **2007**, *9*, 438. (g) Yamaguchi, K.; Kotani, M.; Kamata, K.; Mizuno, N. *Chem. Lett.* **2008**, *37*, 1258. (h) Babu, G.; Orita, A.; Otera, J. *Chem. Lett.* **2008**, *37*, 1296. (i) Cernak, T. A.; Lambert, T. H. *J. Am. Chem. Soc.* **2009**, *131*, 3124.

(3) (a) Suga, S.; Yamada, D.; Yoshida, J. *Chem. Lett.* **2010**, *39*, 404. (b) Yoshida, J.; Saito, K.; Nokami, T.; Nagaki, A. *Synlett* **2011**, 1189.

(4) For example, see: Lenoir, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 3206.

(5) Recent reviews: (a) Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527. (b) Lund, H. *J. Electrochem. Soc.* **2002**, *149*, S21. (c) Sperry, J. B.; Wright, D. L. *Chem. Soc. Rev.* **2006**, *35*, 605. (d) Yoshida, J.; Kataoka, K.; Horcajada, R.; Nagaki, A. *Chem. Rev.* **2008**, *108*, 2265.

(6) Recent examples: (a) Hayashi, K.; Kim, S.; Chiba, K. *Electrochemistry* **2006**, *74*, 621. (b) Wu, X.; Dube, M. A.; Fry, A. J. *Tetrahedron Lett.* **2006**, *47*, 7667. (c) Mitsudo, K.; Kaide,

T.; Nakamoto, E.; Yoshida, K.; Tanaka, H. *J. Am. Chem. Soc.* **2007**, *129*, 2246. (d) Horii, D.; Fuchigami, T.; Atobe, M. *J. Am. Chem. Soc.* **2007**, *129*, 11692. (e) Park, Y. S.; Little, R. D. *Electrochim. Acta* **2009**, *54*, 5077. (f) Kakiuchi, F.; Kochi, T.; Mutsutani, H.; Kobayashi, N.; Urano, S.; Sato, M.; Nishiyama, S.; Tanabe, T. *J. Am. Chem. Soc.* **2009**, *131*, 11310. (g) Kirste, A.; Schnakenburg, G.; Stecker, F.; Fischer, A.; Waldvogel, S. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 971. (h) Ishiguro, Y.; Inagi, S.; Fuchigami, T. *J. Am. Chem. Soc.* **2012**, *134*, 4034.

(7) Swern−Moffatt type oxidation: Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

(8) Kornblum oxidation: Kornblum, N.; Powers, J. W.; Anderson, G. J.; Jones, W. J.; Larson, H. O.; Levand, O.; Weaver, W. M. *J. Am. Chem. Soc.* **1957**, *79*, 6562.

(9) Selected examples of *N*-acyliminium ion pools: (a) Yoshida, J.; Suga, S.; Suzuki, S.; Kinomura, N.; Yamamoto, A.; Fujiwara, K. *J. Am. Chem. Soc.* **1999**, *121*, 9546. (b) Suga, S.; Okajima, M.; Fujiwara, K.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 7941. (c) Suga, S.; Watanabe, M.; Yoshida, J. *J. Am. Chem. Soc.* **2002**, *124*, 14824. (d) Yoshida, J.; Suga, S. *Chem.−Eur. J.* **2002**, *8*, 2651. (e) Maruyama, T.; Mizuno, Y.; Shimizu, I.; Suga, S.; Yoshida, J. *J. Am. Chem. Soc.* **2007**, *129*, 1902.

(10) Selected examples of alkoxycarbenium ion pools: (a) Suga, S.; Suzuki, S.; Yamamoto, A.; Yoshida, J. *J. Am. Chem. Soc.* **2000**, *122*, 10244. (b) Okajima, M.; Suga, S.; Itami, K.; Yoshida, J. *J. Am. Chem. Soc.* **2005**, *127*, 6930. (c) Suga, S.; Matsumoto, K.; Ueoka, K.; Yoshida, J. *J. Am. Chem. Soc.* **2006**, *128*, 7710.

(11) Selected examples of diarylcarbenium ion pools: (a) Okajima, M.; Soga, K.; Nokami, T.; Suga, S.; Yoshida, J. *Org. Lett.* **2006**, *8*, 5005. (b) Nokami, T.; Ohata, K.; Inoue, M.; Tsuyama, H.; Shibuya, A.; Soga, K.; Okajima, M.; Suga, S.; Yoshida, J. *J. Am. Chem. Soc.* **2008**, *130*, 10864. (c) Okajima, M.; Soga, K.; Watanabe, T.; Terao, K.; Nokami, T.; Suga, S.; Yoshida, J. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 594.

(12) (a) Phan, T. B.; Nolte, C.; Kobayashi, S.; Ofial, A. R.; Mayr, H. *J. Am. Chem. Soc.* **2009**, *131*, 11392. A reaction of benzyl cations with DMSO has also been reported in the literature. See: (b) Scheit, K. H.; Kampe, W. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 787.

(13) Tabatabaeian, K.; Mamaghani, M.; Mahmoodi, N. O.; Khorshidi, A. *Catal. Commun.* **2008**, *9*, 416. For other methods of oxidizing alkenes to 1,2-diketones, see: Manandhar, S.; Singh, R. P.; Eggers, G. V.; Shreeve, J. M. *J. Org. Chem.* **2002**, *67*, 6415.

(14) (a) Halas, S. M.; Okyne, K.; Fry, A. *J. Electrochim. Acta* **2003**, *48*, 1837. (b) Bäumer, U.-St.; Schäfer, H. J. *J. Appl. Electrochem.* **2005**, *35*, 1283.

(15) Shono, T.; Matsumura, Y.; Hashimoto, T.; Hibino, K.; Hamaguchi, H.; Aoki, T. *J. Am. Chem. Soc.* **1975**, *97*, 2546.

(16) (a) Matthews, M. A. *Pure Appl. Chem.* **2001**, *73*, 1305. (b) Rusling, J. F. *Pure Appl. Chem.* **2001**, *73*, 1895. (c) Mentel, M.; Beier, M. J.; Breinbauer, R. *Synthesis* **2009**, 1463; and

references cited therein.

(17) Matsumoto, K.; Fujie, S.; Ueoka, K.; Suga, S.; Yoshida, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 2506.

(18) SDBS Web: http://riodb01.ibase.aist.go.jp/sdbs/ (National Institute of Advanced Industrial Science and Technology, February 3, 2011).

(19) Ren, W.; Xia, Y.; Ji, S.-J.; Zhang, Y.; Wan, X.; Zhao, J. *Org. Lett.* **2009**, *11*, 1841.

(20) Chan, C.-L.; Kumar, M. P.; Liu, R.-S. *J. Org. Chem.* **2004**, *69*, 2793.

Chapter 2

Integration of Electrooxidative Cyclization and Chemical Oxidation *via* Alkoxysulfonium Ions

Abstract

An integration of electrooxidative cyclization and chemical oxidation was achieved. Electrochemical oxidation of alkenes having a nucleophilic moiety in the presence of DMSO gave cyclized alkoxysulfonium ions, which were converted to the corresponding ketones by treatment with triethylamine in a one-pot sequential manner. The method was also an effective tool for cyclization of 1,6-dienes affording five-membered ring diketones in high stereoselectivity

Introduction

Alkene vicinal difunctionalization that involves bond forming reactions with nucleophiles and/or electrophiles at two adjacent sp^2 carbons of an alkene serves as a powerful method for organic synthesis, because such transformations rapidly increase molecular complexity.[1,2] In particular, difunctionalization involving an intramolecular attack of a nucleophilic/electrophilic moiety serves as a powerful method for constructing cyclic structures, which appear in a broad array of natural products and biologically active compounds.[3]

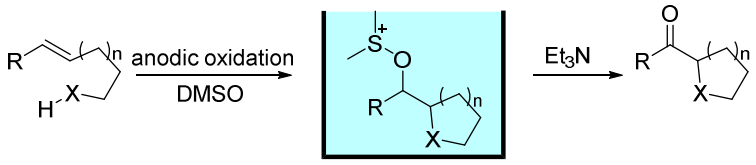
Electrochemical oxidation[4,5] is an effective tool for activating a carbon−carbon double bond of alkenes in an oxidative manner. Such activation sometimes triggers cyclization with a nucleophilic moiety in the molecule to build a cyclic structure.[6] In fact, it is well known that electrochemical oxidation of electron-rich alkenes bearing a nucleophilic moiety, such as a hydroxyl group, an amino group, and an electron-rich aromatic group in an appropriate position, gives the corresponding cyclized products.[7] Anodic oxidation also provides an olefin−olefin coupling reaction in both intramolecular[8] and intermolecular[9] manner. Both the umpolung nature of the reactions that provides new opportunities for generating bonds from existing functional groups and the preservation of functionality that can be employed in subsequent synthetic transformations suggest that the reactions have significant potential for constructing complex molecules.

However, electrochemically generated cyclized products are often further oxidized to give by-products (overoxidation), because the products are exposed to electrochemical oxidative conditions.[7a] Such overoxidation lowers the yields of desired products and the current efficiency. To avoid such a formidable problem, much effort has been devoted so far. One solution is to use controlled potential electrolysis conditions, if the starting material has a lower oxidation potential than the corresponding product.[4a] However, the development of a new method that is generally applicable to electrooxidative cyclization of a wide range of alkenes is strongly needed.

The tactic using dimethyl sulfoxide (DMSO) as an external nucleophile described in Chapter 1[10] serves as a solution to avoid the problem of overoxidation (Scheme 1). The initial one electron oxidation of a carbon–carbon double bond followed by an intramolecular attack of a nucleophilic moiety and subsequent one electron oxidation leads to a cyclized cationic intermediate. The use of DMSO as a nucleophile gives a cationic alkoxysulfonium intermediate. A positive charge on sulfur raises the oxidation potential, and therefore overoxidation is suppressed. There is another advantage of this tactics; the alkoxysulfonium ion intermediate can be converted to ketones by treatment with triethylamine *via* Swern–Moffatt type oxidation.[11] Thus, integration[12,13] of electrochemical oxidative cyclization of alkenes and the chemical oxidation of the resulting alkoxysulfonium ions leads to the formation of cyclized ketones, serving as an intriguing transformation that is useful for organic synthesis. This chapter focuses on the integration of

electrooxidative cyclization of alkenes in the presence of DMSO and chemical oxidation of the resulting alkoxysulfonium ions to give cyclized ketones.

Scheme 1. Oxidation of Alkenes by Integration of Electrochemical Method and Chemical Method *via* Alkoxysulfonium Ions.



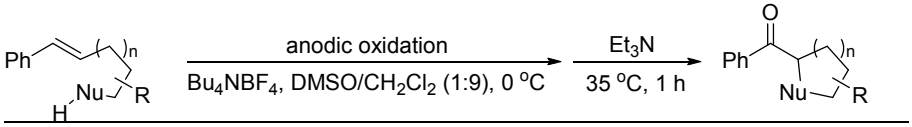
Results and Discussions

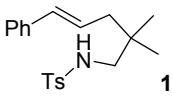
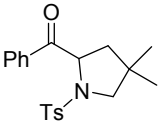
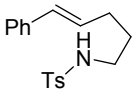
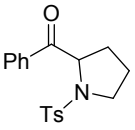
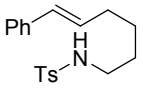
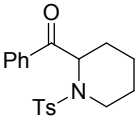
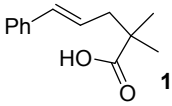
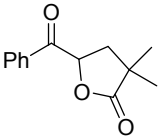
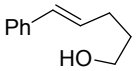
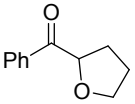
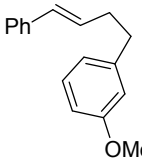
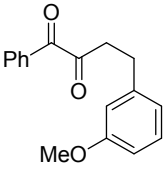
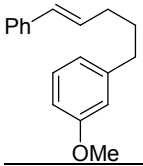
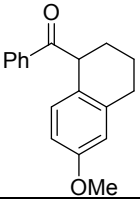
Oxidative cyclization of alkenes having nucleophilic functional groups

β-Alkylstyrenes bearing various nucleophilic functional groups were chosen to use as cation precursors. To achieve selective oxidation of alkenes in the presence of DMSO, the oxidation potentials of alkenes should be lower than that of DMSO (1.76 V vs. SCE). Therefore, the oxidation potentials of alkenes were determined using rotating disk electrode (RDE) voltammetry.[14] The oxidation potentials of β-alkylstyrenes having a nucleophilic moiety, such as a tosylamide group (**1a** 1.34 V, **1b** 1.31 V, **1c** 1.38 V), are lower than that of DMSO (Table 1). Because the oxidation potentials of tosylamides such as propyl tosylamine (1.90 V) are higher than **1a**–**1c**, the alkene part seems to be oxidized without affecting the tosylamide moiety. The fact that the oxidation potentials of **1a**–**1c** are lower than those of simple styrenes such as β-methylstyrene (1.42 V) indicates that the radical cation generated by one-electron oxidation is stabilized by the interaction with the nucleophilic moiety.[8d] It is also interesting that the oxidation potentials of **1a** and **1b**, having three methylene groups between the alkene moiety and the nitrogen atom, were less positive than that of **1c** having four methylene groups.

With the information on oxidation potentials in hand, integrated electrooxidative cyclization and chemical oxidation of **1a**–**1c** were carried out. For example, **1a** was anodically oxidized at constant current (8 mA) in DMSO/CH_2Cl_2 (1:9) using Bu_4NBF_4 as a supporting electrolyte at 0 ^oC in an H-type divided cell equipped with an anode consisting of fine fibers made from carbon felt and a platinum plate cathode until 2.1 F/mol of electricity was consumed. Treatment of the resulting solution with triethylamine (Et_3N) gave the corresponding ketone with a five-membered ring (**3a**) in 89% yield (Table 1).

Table 1. Integrated Electrooxidative Cyclization Followed by Chemical Oxidation of Alkenes Bearing a Nucleophilic Moiety.[a]



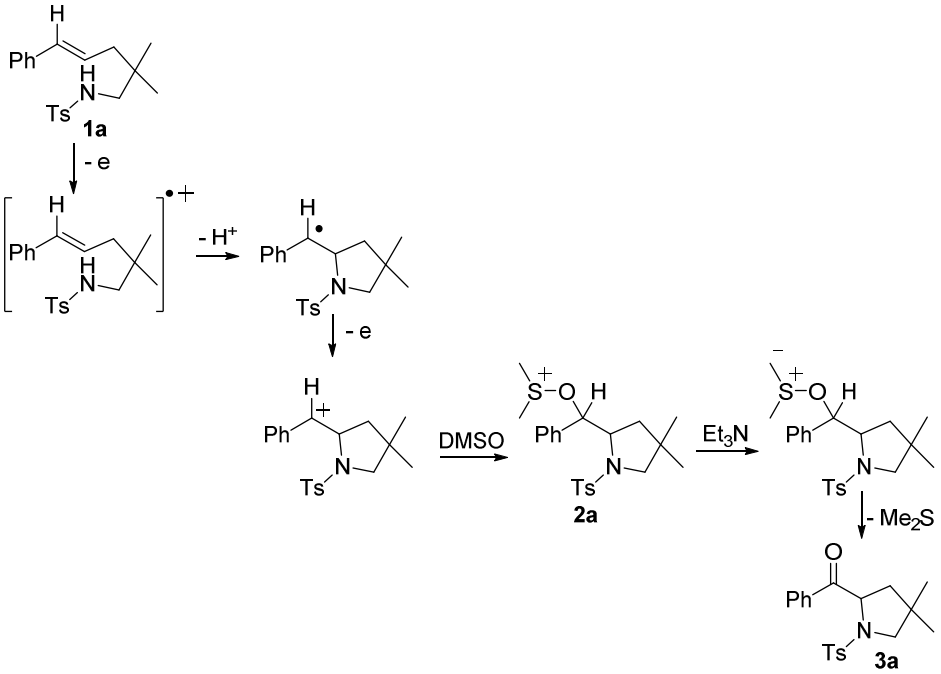
Substrate	Oxidation Potential (V)[b]	Electricity (F/mol)	Product	Yield (%)[c]
 **1a**	1.34	2.1	 **3a**	89
 **1b**	1.31	2.5	 **3b**	85
 **1c**	1.38	2.1	 **3c**	13
 **1d**	--[d]	2.1	 **3d**	61
 **1e**	1.20	3.0	 **3e**	52[e]
 **1f**	1.30	3.0	 **3f**	23
 **1g**	1.21	2.1	 **3g**	73

[a]Reactions were carried out with 0.25 mmol of **1**, 10 mL of $DMSO/CH_2Cl_2$ (1:9), and 0.3 M Bu_4NBF_4. [b]Oxidation potentials were determined by RDE voltammetry in 0.1 M $LiClO_4/CH_3CN$ using SCE as a reference electrode. [c]Yields of isolated products after purification on silica gel. [d]The oxidation potential could not be determined under the conditions because high noise overlapped. [e]$DMSO/CH_2Cl_2$ (1:2) was used as a solvent.

The mechanism shown in Scheme 2 seems to be reasonable. One-electron oxidation of **1a** gives the radical cation. A nucleophilic attack of the nitrogen atom of the tosylamine moiety followed by deprotonation gives the cyclized benzylic radical, which is further oxidized to give

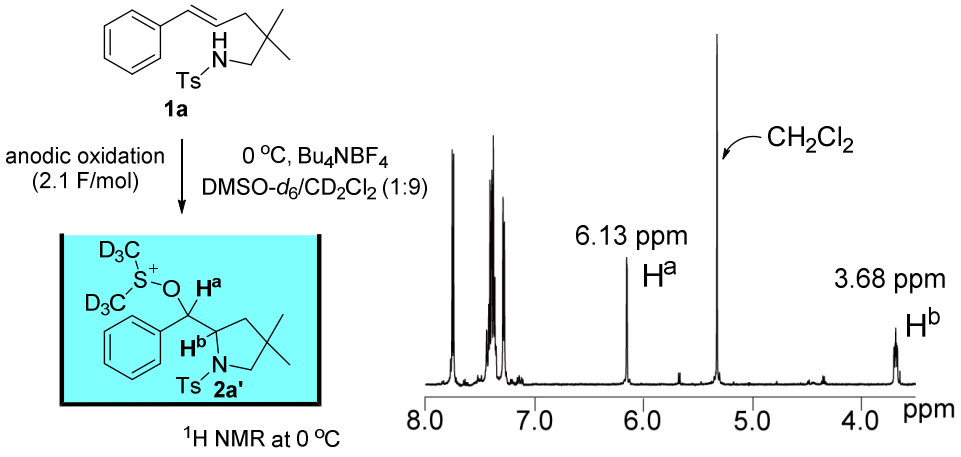
the benzylic cation. An attack of DMSO gives the cyclized alkoxysulfonium ion **2a** as a cation pool.[15] Treatment of **2a** with triethylamine gives the sulfur ylide, and an intramolecular proton transfer followed by the elimination of dimethylsulfide (Me_2S) gives the cyclized ketone **3a**.

Scheme 2. A Mechanism of the Formation of Cyclized Alkoxysulfonium Ion **2**.



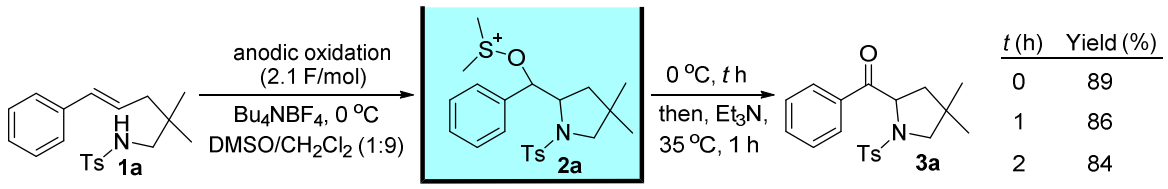
The generation of the cyclized alkoxysulfonium ion by electrooxidative cyclization was directly observed by ^{1}H NMR analysis.[16] Electrochemical oxidation of **1a** was carried out in the presence of DMSO-d_6 at 0 °C in an H-type divided cell, and the ^{1}H NMR spectrum of the resulting solution indicated that the cyclized alkoxysulfonium ion was generated (Scheme 3).

Scheme 3. Low Temperature NMR Analysis of Cyclized Alkoxysulfonium Ion **2a'**.



Thermal stability of alkoxysulfonium ion **2a** was studied. A pool of **2a** was generated from **1a** and was stirred at 0 °C for a certain time (t hour). Then **2a** was treated with triethylamine at 35 °C for 1 hour, and the yield of **3a** was determined. The results shown in Scheme 4 indicate that **2a** is stable at 0 °C within a few hours.

Scheme 4. Thermal Stability of Alkoxysulfonium Ion **2a'** and Its Thermal Stability.



t (h)	Yield (%)
0	89
1	86
2	84

Anodic oxidation of **1b** in DMSO/CH_2Cl_2 followed by treatment with triethylamine also took place smoothly and the corresponding cyclized product **4b** was obtained in 85% yield. The reaction of **1c** gave the corresponding cyclized product **4c**, but the yield was low. Significant amounts of a mixture of unidentified products were obtained. The higher oxidation potential of **1c** compared with those of **1a** and **1b** indicating smaller interaction of the tosylamide moiety with the radical cation of the alkene moiety giving rise to less effective cyclization seems to be responsible (*vide supra*). The formation of a five-membered ring seems to be more favorable than the formation of a six-membered ring.[4a]

The cyclization is also effective for the carboxylic acid moiety and hydroxyl group as an intramolecular nucleophile. Thus, anodic oxidation of **1d** in DMSO/CH_2Cl_2 followed by treatment with triethylamine afforded the corresponding cyclized products **3d**, whereas the electrochemical oxidation of **1e** in the presence of DMSO gave the corresponding cyclized product **3e**. Therefore, the present method is useful for synthesis of lactone and tetrahydrofuran derivatives.

It seems to be reasonable to consider that aromatic groups can be used as nucleophilic moieties. However, anodic oxidation of **1f** having an 3-anisyl group as a nucleophilic moiety followed by treatment with triethylamine gave 1,2-diketone **4f** in 23% yield and no cyclized product was obtained. Five-membered ring cyclization is not effective in this case. In contrast, anodic oxidation of **1g** followed by treatment with triethylamine gave the cyclized ketone **3g** in 73% yield. The corresponding 1,2-diketone was not detected. Six-membered ring cyclization took place effectively. This is consistent with the fact that the oxidation potential of **1g** is lower than that of **1f**. The oxidation potentials of **1f** and **1g** were lower than that of 3-methoxytoluene, indicating that the initial one-electron oxidation took place at the alkene moiety to give the corresponding radical cation intermediates. In this case, the interaction to form a six-membered ring is more favorable than that to form a five-membered ring, presumably because sp^2 carbons

are involved in the ring (Fig. 1).

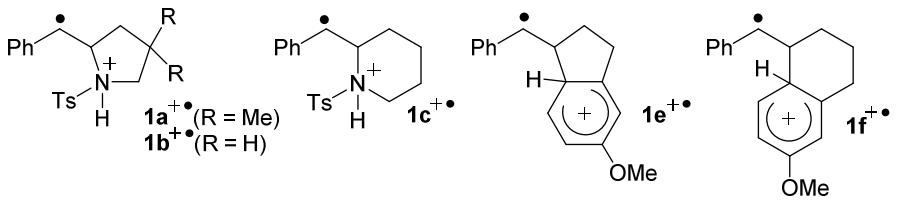


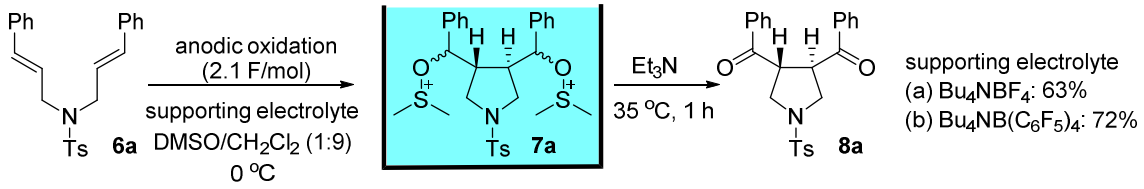
Figure 1. Proposed configuration of cation radicals.

Oxidative cyclization of 1,6-dienes

Next, the electrochemical oxidation of 1,6-dienes for intramolecular alkene−alkene coupling (diene cyclization) was investigated, because the radical cation generated from one of the carbon−carbon double bond is expected to react with the other carbon−carbon double bond. To test the feasibility of the electrochemical diene cyclization, compound **6a** was chosen as a substrate. The oxidation potential of **6a** (1.16 V) was less positive than that of DMSO (1.76 V), indicating that **6a** can be selectively oxidized in the presence of DMSO.[14] Moreover, the oxidation potential of **6a** is lower than that of *N*-cinnamyl-*N*-methyltosylamide, a mono-olefinic compound (1.54 V), indicating interaction between two carbon–carbon double bonds in the radical cation generated by one-electron oxidation of **6a**.

Thus, the reaction of diene **6a** in the presence of DMSO was examined. Electrochemical oxidation of **6a** in DMSO/CH_2Cl_2 (1:9) using Bu_4NBF_4 as a supporting electrolyte at 0 °C followed by treatment with triethylamine gave the corresponding diketone **8a** in 63% yield as a single diastereomer (Scheme 4(a)). The generation of bisalkoxysulfonium ion **7a** is strongly suggested. The yield of **8a** increased to 72% when $Bu_4NB(C_6F_5)_4$ was used as a supporting electrolyte (Scheme 4(b)).

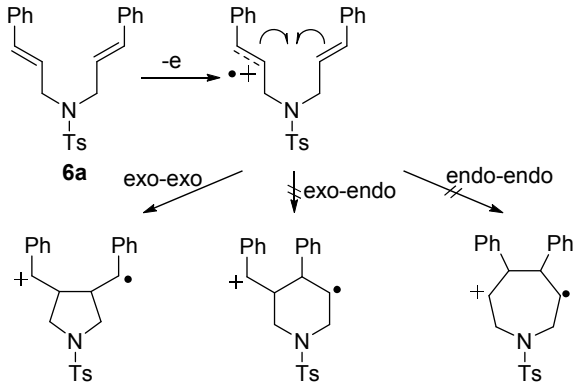
Scheme 4. Integration of Electrooxidative Cyclization and Chemical Oxidation of 1,6-Diene **6a**.



The formation of **8a**, which contains a five-membered ring, indicates that the cyclization step proceeded in an exo–exo manner,[9] although exo–endo and endo–endo cyclizations lead to six- and seven-membered ring products, respectively (Scheme 5). Presumably, cyclization to form benzylic cation and benzylic radical species simultaneously is favorable. Stereoelectronic effects

also seem to play an important role.

Scheme 5. Electrooxidative Cyclization of 1,6-Diene **6a**.



The X-ray single crystal structure analysis of **8a** indicated *trans* stereochemistry. To get a deeper insight into the stereoselectivity, DFT calculations of a model system, such as the cation radical of (*E*,*E*)-1,7-diphenyl-1,6-heptadiene, were carried out.[17] The geometry optimization indicated that conformer **A**, which leads to a *trans* cyclized cation radical, is more stable than conformer **B**, which leads to a *cis* cyclized cation radical (Fig. 2).[18] The results are consistent with the observed stereoselectivity.

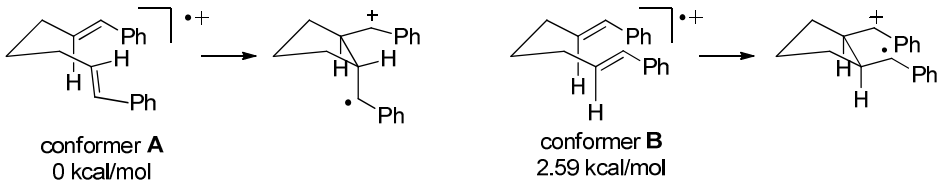
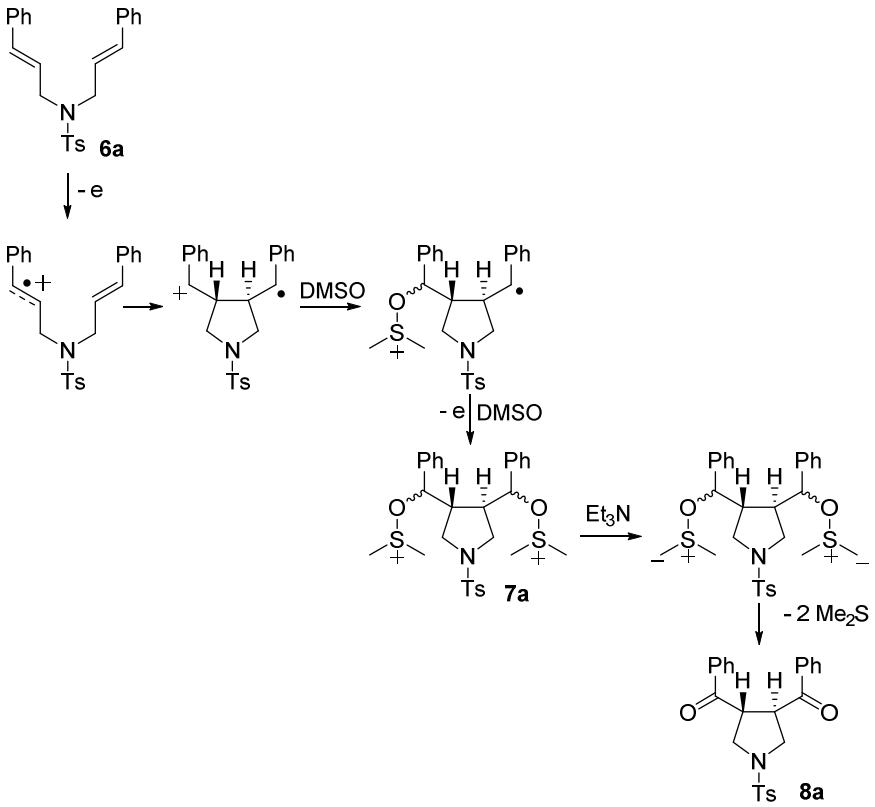


Figure 2. Energies of two conformers of the cation radical of (*E*,*E*)-1,7-diphenyl-1,6-heptadiene obtained by DFT calculations on the B3LYP/6-31+G(d) level.

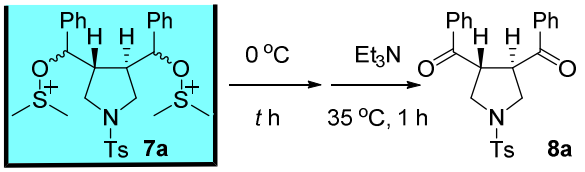
The following mechanism seems to be reasonable (Scheme 6). The cyclized radical cation reacts with DMSO to form a radical containing an alkoxysulfonium ion moiety. Further oxidation followed by trapping with DMSO gives a bisalkoxysulfonium ion **7a**. Treatment of **7a** with triethylamine leads to Swern–Moffatt type oxidation to give **8a**.

Scheme 6. A Mechanism of the Formation of Cyclized Diketone **8a**.



Thermal stability of the bisalkoxysulfonium ion **7a** was studied (Scheme 7). A pool of **7a** was stirred at 0 °C for a certain time (t hours). Then triethylamine was added, and the resulting mixture was stirred at 35 °C for 1 hour. As shown in Scheme 8, **7a** gradually decomposed at 0 °C. The lower stability of **7a** compared to **2a** can be attributed to the dicationic character of **7a**.

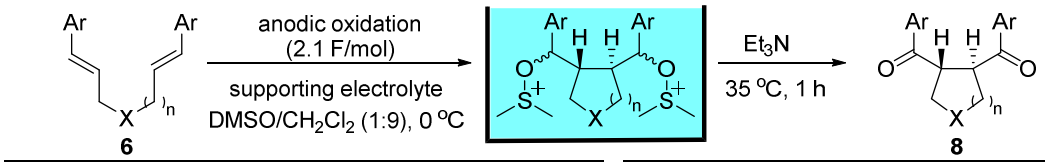
Scheme 7. Thermal Stability of Bisalkoxysulfonium ion **7a**.

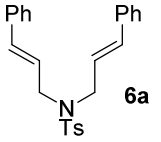
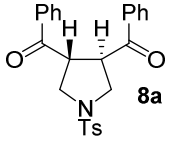
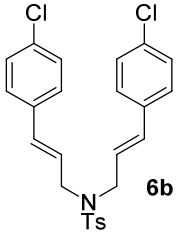
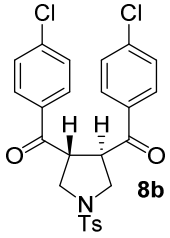
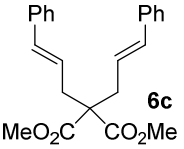
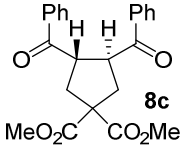
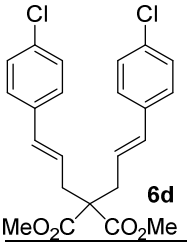
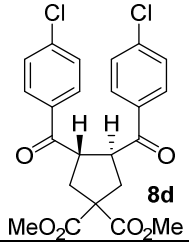
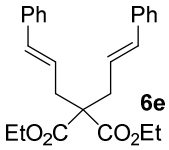
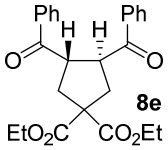
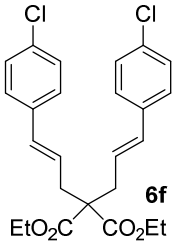
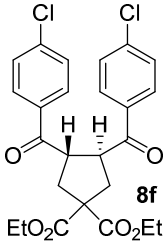
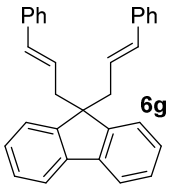
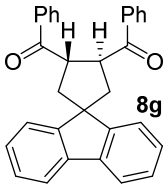
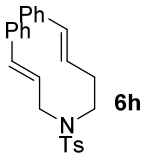
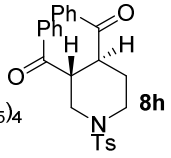


t (h)	Yield (%)
0	72
1	50
2	41

The present integrated diene cyclization followed by chemical oxidation is applicable to various dienes (Table 2). The malonate bridge is also effective. Anodic oxidation of **6c**, **6d**, **6e**, and **6f** in DMSO/CH_2Cl_2 followed by treatment with triethylamine gave the corresponding cyclized diketones (**8c**–**8f**). A diene having a fluorene bridge (**6g**) also gave the corresponding cyclized diketone **8g**.

Table 2. Integration of Electrooxidative Cyclization and Chemical Oxidation of Dienes[a].



Diene **6**	Supporting electrolyte	Product **8**	Yield (%)[b]
 **6a**	Bu_4NBF_4	 **8a**	63[c]
	$Bu_4NB(C_6F_5)_4$		72
 **6b**	$Bu_4NB(C_6F_5)_4$	 **8b**	90
 **6c**	Bu_4NBF_4	 **8c**	54
 **6d**	Bu_4NBF_4	 **8d**	71
 **6e**	Bu_4NBF_4	 **8e**	54
 **6f**	Bu_4NBF_4	 **8f**	71
 **6g**	Bu_4NBF_4	 **8g**	72
 **6h**	$Bu_4NB(C_6F_5)_4$	 **8h**	45

[a]Reactions were carried out with 0.13 mmol scale according to the conditions of Scheme 4. [b]Yields of the isolated products after purification on silica gel. [c]Yields determined by ^{1}H NMR using tetrachloroethane as an internal standard.

The present integrated electrooxidative cyclization followed by chemical oxidation can also be applied to 1,7-dienes. For example, the reaction of 1,7-diene **6h** led to exo–exo cyclization to give diketone **8h** as a single stereoisomer, although the yield was moderate. The higher oxidation potential of **6h** (1.36 V) than that of **6a** indicates that the intramolecular interaction of the two alkene moieties in the radical cation of **6h** is less effective than that in the cation radical of **6a**.

Conclusion

In conclusion it was found that alkoxysulfonium ions effectively mediate the integration of

electrooxidative cyclization and chemical oxidation of alkenes having a nucleophilic moiety in an appropriate position. A similar transformation is also applicable to 1,6-dienes and 1,7-dienes. DMSO effectively traps the cyclized cation or cation radical to generate cyclized alkoxysulfonium ions, which are sufficiently stable at low temperatures. The subsequent treatment with triethylamine gives rise to Swern–Moffatt type oxidation to give the corresponding carbonyl compounds. Because the products are not subjected to electrochemical oxidation, the problem of overoxidation is avoided. Because the carbonyl functionality can be used for further transformations, the present method serves as a useful tool for synthesis of organic compounds having cyclic structures. It is hoped that the present achievement opens a new aspect of electroorganic synthesis.

Experimental Section

General Remarks. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian MERCURY plus-400 (^{1}H 400 MHz, ^{13}C 100 MHz), or a JEOL ECA-600P spectrometer (^{1}H 600 MHz, ^{13}C 150 MHz). 1,1,2,2-Tetrachloroethane (TCE) was used as an internal standard for NMR yield (^{1}H NMR, 5.95 ppm, 2 H). Mass spectra were obtained on a JEOL EXACTIVE, and on a JEOL JMS SX-102A mass spectrometer. IR spectra were measured on a Shimadzu IRAffinity (FTIR). Merck precoated silica gel F254 plates (thickness 0.25 mm) were used for thin-layer chromatography (TLC) analysis. Flash chromatography was performed with silica gel (Kanto Chem. Co., Silica Gel N, spherical, neutral, 40–100 mm). Preparative gel permeation chromatography (GPC) was carried out on a Japan Analytical Industry LC-918 equipped with JAIGEL-1H and 2H using $CHCl_3$ as an eluent. Rotating disk electrode (RDE) voltammetry was carried out using a BAS 600C electrochemical analyzer and the BAS RRDE-3 electrode apparatus. Measurements were carried out in 0.1 M $LiClO_4/CH_3CN$ using a glassy carbon disk working electrode, a platinum wire counter electrode, and an SCE reference electrode with a sweep rate of 10 mV s^{-1} at 3000 rpm. X-ray single crystal structure analysis was performed on a RIGAKU R-AXIS RAPID. All reactions were carried out under an argon atmosphere unless otherwise noted. Anodic oxidations were carried out using an H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon JF-20-P21E, ca. 160 mg for 0.25 mmol scale or ca. 80 mg for 0.13 mmol scale, dried at 300 ^{o}C/1 mmHg for 4 hours before use) and a platinum plate cathode (10 mm × 10 mm).

Materials. Compounds **1a**,[19] **1b**,[19] **1c**,[20] **1d**,[21] **1e**,[22] 4-(3-anisyl)-1-butene,[4a] and *N*-tosylpropylamine,[23] were prepared according to the reported procedures. Bu_4NBF_4 was purchased from TCI and dried at 50 ^{o}C/1 mmHg for 12 hours. $Bu_4NB(C_6F_5)_4$ was prepared according to the reported procedure.[24] Dichloromethane was washed with water, distilled from P_2O_5, redistilled from dried K_2CO_3 to remove trace amounts of acid, and stored over molecular sieves 4A. Triethylamine (Et_3N) was refluxed with calcium hydride, distilled, and stored over molecular sieves 4A. CD_2Cl_2 was dried over molecular sieves 4A before use. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. DFT calculations were performed with the Gaussian 09 program.[17] All geometry optimizations were carried out at the RB3LYP or UB3LYP level of density functional theory with the 6-31+G(d) basis set.

Preparation of (*E*)-1-phenyl-4-(3-anisyl)-1-butene (1f). To a round-bottom flask were added benzylidenebis(tricyclohexylphosphine)dichlororuthenium (the 1st generation Grubbs catalyst) (100 mg, 0.12 mmol), 4-(3-anisyl)-1-butene (800 mg, 4.93 mmol), styrene (1.1 g, 10.6 mmol), and CH_2Cl_2 (20 mL). Then, the mixture was heated to 40 °C and stirred for an additional 96 hours. The solvent was removed under reduced pressure and the resulting crude product was

purified with flash chromatography (hexane/EtOAc 20 : 1) to obtain the title compound (440 mg, 36%): TLC R_f 0.44 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.53 (q, *J* = 7.2 Hz, 2 H), 2.77 (dd, *J* = 7.2, 8.4 Hz, 2 H), 3.80 (s, 3 H), 6.26 (dt, *J* = 6.8, 15.6 Hz, 1 H), 6.43 (d, *J* = 16.0 Hz, 1 H), 6.77 (m, 2 H), 6.83 (d, *J* = 8.0 Hz, 1 H), 7.27 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.8, 35.9, 55.1, 111.2, 114.2, 120.9, 126.0, 126.9, 128.5, 129.3, 129.9, 130.4, 137.7, 143.4, 159.6; HRMS (ESI) calcd for $C_{17}H_{19}O$ [M+H$^+$]: 237.1285, found: 237.1284.

Preparation of (*E*)-1-phenyl-5-(3-anisyl)-1-pentene (1g). To a round-bottom flask were added 3-methoxyphenethyl bromide (1.05 g, 4.88 mmol), CuI (0.5 g, 2.6 mmol), and THF (40 mL). The solution was cooled to 0 ^{o}C. A solution of allyl magnesium bromide in diethyl ether (1.0 M, 10 mL, 10 mmol) was added and the reaction mixture was allowed to warm to room temperature. After 12 hours, water was added and the solution was extracted with EtOAc (20 mL x 3), washed with brine (20 mL x 3), dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified with flash chromatography (hexane/EtOAc 15:1) to obtain **5-(3-anisyl)-1-pentene** (720 mg, 84%): TLC R_f 0.55 (hexane/EtOAc 5:1). The spectra were in agreement with the literature.[25]

To a round-bottom flask were added 5-(3-anisyl)-1-pentene (126 mg, 0.715 mmol), benzylidenebis(tricyclohexylphosphine)dichlororuthenium (the 1st generation Grubbs catalyst) (52 mg, 0.063 mmol), styrene (156 mg, 1.50 mmol), and CH_2Cl_2 (2.5 mL). Then, the mixture was heated to 40 ^{o}C and stirred for additional 30 hours. The solvent was removed under reduced pressure and the resulting crude product was purified with flash chromatography (hexane/EtOAc 50:1) to obtain **(*E*)-1-phenyl-5-(3-anisyl)-1-pentene** (**1g**) (120 mg, 67%): TLC R_f 0.61 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82 (tt, *J* = 7.2, 7.6 Hz, 2 H), 2.27 (dt, *J* = 6.8, 7.2 Hz, 2 H), 2.67 (t, *J* = 7.6 Hz, 2 H), 3.81 (s, 3 H), 6.25 (dt, *J* = 6.8, 15.6 Hz, 1 H), 6.41 (d, *J* = 15.6 Hz, 1 H), 6.75 (m, 2 H), 6.80 (d, *J* = 6.4 Hz, 1 H), 7.20 (m, 2 H), 7.32 (m, 4 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 30.9, 32.5, 35.4, 55.1, 111.0, 114.2, 120.9, 125.9, 126.8, 128.4, 129.2, 130.2, 130.5, 137.8, 144.0, 159.6; IR (neat) 1584.1, 1601.5, 2938.7, 3010.1 cm^{-1}; LRMS (EI) *m/z* 253 [M+H$^+$], 252 [M$^+$]; HRMS (EI) calcd for $C_{18}H_{20}O$ [M$^+$]: 252.1514, found: 252.1519.

Typical procedure for the oxidation of alkenes bearing a nucleophilic functional group. In the anodic chamber were placed 0.25 mmol of the alkene having the nucleophilic functional group, Bu_4NBF_4 (980 mg, 3.0 mmol), DMSO (1.0 mL) and CH_2Cl_2 (9.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (55 μL, 0.62 mmol), Bu_4NBF_4 (980 mg, 3.0 mmol), and CH_2Cl_2 (10.0 mL). A constant current electrolysis (8.0 mA) was carried out at 0 ^{o}C with magnetic stirring until TLC analysis indicated that the alkene was consumed. Then 0.5 mL of Et_3N was added to both the anodic and the cathodic chambers, and the resulting mixture was heated at 35 ^{o}C with stirring for 1 hour. After removal of the solvent of the anodic solution under

reduced pressure, the residue was quickly filtered through a short column (2 x 4 cm) of silica gel to remove Bu_4NBF_4 using hexane/EtOAc (1:1) containing 1 vol% of triethylamine as an eluent. Purification of the crude product by flash chromatography gave the cyclized carbonyl compounds.

***N*-Tosyl-2-benzoyl-4,4-dimethylpyrrolidine (3a).** Electrochemical oxidation (2.1 F/mol) of (*E*)-*N*-tosyl-3,3-dimethyl-5-phenyl-4-pentenamine (**1a**) (85.0 mg, 0.247 mmol) followed by flash chromatography (hexane/EtOAc 4:1) gave the title compound (78.6 mg, 89%): TLC R_f 0.22 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 3 H), 1.05 (s, 3 H), 1.74 (dd, *J* = 8.8, 12.4 Hz, 1 H), 2.10 (dd, *J* = 8.4, 12.8 Hz, 1 H), 2.41 (s, 3 H), 3.17 (d, *J* = 10.0 Hz, 1 H), 3.32 (d, *J* = 9.6 Hz, 1 H), 5.37 (t, *J* = 8.8 Hz, 1 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 7.47 (dd, *J* = 7.2, 7.4 Hz, 2 H), 7.57 (t, *J* = 8.0 Hz, 1 H), 7.80 (d, *J* = 8.0 Hz, 2 H), 7.96 (d, *J* = 7.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 25.3, 26.0, 39.5, 45.3, 60.4, 63.4, 127.7, 128.5, 128.7, 129.5, 133.4, 135.3, 136.3, 143.3, 197.8; IR (neat) 1699.9, 2965.7, 3027.4 cm^{-1}; LRMS (ESI) *m/z* 358 [M+H$^+$], 357 [M$^+$], 252 [(M−C_6H_5CO)$^+$]; HRMS (ESI) calcd for $C_{20}H_{24}O_3NS$ [M+H$^+$]: 358.1471, found 358.1475.

***N*-Tosyl-2-benzoylpyrrolidine (3b).** Electrochemical oxidation (2.5 F/mol) of (*E*)-*N*-tosyl-5-phenyl-4-pentenamine (**1b**) (78.5 mg, 0.249 mmol) followed by flash chromatography (hexane/EtOAc 10:3) gave the title compound (70.0 mg, 85%): TLC R_f 0.27 (hexane/EtOAc 10:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80–2.02 (m, 3 H), 2.20 (m, 1 H), 2.42 (s, 3 H), 3.48 (t, *J* = 6.4 Hz, 2 H), 5.38 (dd, *J* = 3.2, 8.8 Hz, 1 H), 7.31 (d, *J* = 8.4 Hz, 2 H), 7.48 (dd, *J* = 7.6, 7.6 Hz, 2 H), 7.59 (t, *J* = 7.6 Hz, 1 H), 7.77 (d, *J* = 8.0 Hz, 2 H), 7.97 (d, *J* = 7.6 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5, 24.6, 30.8, 48.2, 62.9, 127.5, 128.5, 128.7, 129.5, 133.4, 134.8, 135.9, 143.4, 197.4; IR (neat) 1323.2, 1693.8 cm^{-1}; LRMS (ESI) *m/z* 330 [M+H$^+$], 347 [M+NH_4^+]; HRMS (ESI) calcd for $C_{18}H_{20}O_3NS$ [M+H$^+$]: 330.1158, found 330.1147.

***N*-Tosyl-2-benzoylpiperidine (3c).** Electrochemical oxidation (2.1 F/mol) of (*E*)-*N*-tosyl-6-phenyl-5-hexenamine (**1c**) (40.0 mg, 0.121 mmol) followed by flash chromatography (hexane/EtOAc 3:1 with 1 vol% of Et_3N) gave the title compound (5.5 mg, 13%): TLC R_f 0.21 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53–2.41 (m, 6 H), 2.41 (s, 3 H), 2.84 (t, *J* = 7.2 Hz, 1 H), 2.97 (q, *J* = 6.4 Hz, 1 H), 4.56 (m, 1 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 7.49 (t, *J* = 7.2 Hz, 2 H), 7.65 (t, *J* = 7.2 Hz, 1 H), 7.74 (d, *J* = 8.8 Hz, 2 H), 7.95 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6, 21.5, 29.0, 37.9, 42.7, 127.1, 128.9, 129.7, 130.2, 131.8, 134.7, 136.9, 143.5, 192.0, 202.6; HRMS (ESI negative) calcd for $C_{19}H_{20}NO_3S$ [(M−H)$^-$]: 342.1169, found: 342.1162.

3,3-Dimethyl-5-benzoyltetrahydrofuran-2-one (3d). Electrochemical oxidation (2.1 F/mol) of **1d** (49.5 mg, 0.242 mmol) followed by flash chromatography (hexane/EtOAc 4:1) gave the title compound (32.3 mg, 61%): TLC R_f 0.57 (hexane/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 3 H), 1.36 (s, 3 H), 2.41 (m, 2 H), 5.63 (t, *J* = 7.2 Hz, 1 H), 7.50 (d, *J* = 7.2 Hz, 2 H), 7.63 (m, 1 H), 7.98 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 25.6, 39.6, 39.8, 76.1, 129.1, 129.2, 134.2, 134.4, 181.1, 194.9; HRMS (ESI) calcd for $C_{13}H_{14}O_3$ [M+H$^+$]: 219.1016, found: 219.1015.

2-Benzoyltetrahydrofuran (3e). Electrochemical oxidation (3.0 F/mol) of (*E*)-5-phenyl-4-pentenol (**1e**) (40.2 mg, 0.248 mmol) and subsequent treatment with Et_3N followed by flash chromatography (hexane/EtOAc 5:1) gave the title compound (22.6 mg, 52%): TLC R_f 0.39 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97 (m, 2 H), 2.14 (m, 1 H), 2.28 (m, 1 H), 4.00 (m, 2 H), 5.25 (dd, *J* = 5.6, 8.4 Hz, 1 H), 7.46 (m, 2 H), 7.56 (m, 1 H), 7.98 (d, *J* = 7.2 Hz, 2 H). The spectra were in agreement with the literature.[26]

1-Phenyl-4-(3-anysyl)butan-1,2-dione (5f). Electrochemical oxidation (3.0 F/mol) of (*E*)-1-phenyl-4-(3-methoxyphenyl)-1-butene (**1f**) (30.3 mg, 0.127 mmol) followed by flash chromatography (hexane/EtOAc 5:1) gave the title compound (7.8 mg, 23%): TLC R_f 0.33 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.02 (t, *J* = 7.6 Hz, 2 H), 3.23 (t, *J* = 7.2 Hz, 2 H), 3.78 (s, 3 H), 6.73–6.78 (m, 2 H), 6.82 (dd, *J* = 0.4, 7.6 Hz, 1 H), 7.20 (t, *J* = 8.0 Hz, 1 H), 7.47, (t, *J* = 7.6 Hz, 2 H), 7.63 (m, 1 H), 7.92 (dd, *J* = 1.2, 8.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.9, 40.1, 55.1, 111.8, 114.1, 120.7, 128.8, 129.6, 130.2, 131.8, 134.6, 141.7, 159.7, 192.0, 202.2; HRMS (ESI) calcd for $C_{17}H_{17}O_3$ [M+H$^+$]: 269.1172, found: 269.1165.

1-Benzoyl-6-methoxy-1,2,3,4-tetrahydronaphthalene (3g). Electrochemical oxidation (2.1 F/mol) of (*E*)-1- phenyl-5-(3-methoxyphenyl)-1-pentene **(1g)** (30.5 mg, 0.121 mmol) followed by flash chromatography (hexane/EtOAc 20:1 with 1 vol% of Et_3N) gave the title compound (23.5 mg, 73%): TLC R_f 0.36 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.78 (m, 1 H), 1.92 (m, 1 H), 2.07 (m, 1 H), 2.15, (m, 1 H), 2.85, (m, 2 H), 3.79 (s, 3 H), 4.77 (t, *J* = 6.8 Hz, 1 H), 6.68 (m, 2 H), 6.84, (d, *J* = 8.4 Hz, 1 H), 7.49 (dd, *J* = 7.6, 7.6 Hz, 2 H), 7.58 (m, 1 H), 8.01 (dd, *J* = 1.2, 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.6, 27.7, 29.6, 46.7, 55.1, 112.3, 113.9, 126.8, 128.6, 128.7, 130.3, 132.9, 136.6, 138.9, 158.1, 202.8; IR (neat) 1597.6, 1680.6, 2938.7, 3012.0 cm^{-1}; LRMS (ESI) *m/z* 266 [M$^+$]; HRMS (ESI) calcd for $C_{18}H_{18}O_2$ [M$^+$]: 266.1307, found: 266.1296.

Low temperature NMR analysis of alkoxysulfonium ion 2a'. The anodic oxidation was carried out using a divided cell equipped with a carbon felt anode and a platinum plate cathode.

In the anodic chamber were placed (*E*)-*N*-tosyl-3,3-dimethyl-5-phenyl-4-pentenamine (**1a**) (23.5 mg, 0.068 mmol), Bu_4NBF_4 (49 mg, 0.149 mmol), DMSO-d_6, (0.5 mL), and CD_2Cl_2 (4.5 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (12 μL, 0.14 mmol) and 0.1 M Bu_4NBF_4/CD_2Cl_2 (5.0 mL). The constant current electrolysis (4.0 mA) was carried out at 0 ^oC with magnetic stirring until 2.1 F/mol of electricity was consumed. The reaction mixture of the anodic chamber (0.6 mL) was transferred to a 5 mm ϕ NMR tube with septum cap under argon atmosphere at room temperature, and the NMR measurement was carried out at 0 ^oC. Chemical shifts are reported using methylene signals of CH_2Cl_2 at δ 5.32 as an internal standard. Selected signals for **2a'** (3.5−10.0 ppm for ^1H NMR at 0 ^oC, 60.0−200.0 ppm for ^{13}C NMR at 0 ^oC). ^1H NMR (600 MHz, CD_2Cl_2) δ 3.68 (m, 1 H), 6.15 (s, 1 H), 7.28 (d, J = 8.2 Hz, 2 H), 7.39 (m, 5 H), 7.74 (d, J = 8.2 Hz, 2 H); ^{13}C NMR (150 MHz, CD_2Cl_2) δ 62.1, 64.8, 90.3, 125.6, 127.6, 129.1, 129.3, 130.3, 135.0, 145.1.

Preparation of tosylamide-bridged 1,6-diene 6a and 6b. To a round-bottom flask were added sodium hydride (3 equiv.) and DMF, and the mixture was stirred at 0 ^oC. A solution of *p*-toluenesulfonamide (1.0 equiv.) in DMF was slowly added and then cinnamyl bromide or 4-chlorocinnamyl chloride (2.2 equiv.), and the mixture was stirred at 0 ^oC. After 4 hours, water was added at 0 ^oC and the mixture was extracted with hexane/EtOAc (1:1), then the organic extracts were washed by brine. After removal of solvent under reduced pressure, the crude product was purified by flash chromatography or reclystallization to give the tosylamide-brideged 1,6-dienes.

***N*,*N*-dicinnamyl-*N*-tosylamine (6a).** Reaction of *p*-toluenesulfonamide (1.0 g, 5.8 mmol) with cinnamyl bromide (3.3 g, 16.7 mmol), followed by flash chromatography (hexane/EtOAc 1:1), and reclystallization (hexane/EtOAc) gave the title compound (1.91 g, 82%): TLC R_f 0.25 (hexane/EtOAc 5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3 H), 4.01 (d, J = 6.8 Hz, 4 H), 5.98 (dt, J = 6.8 15.6 Hz, 2 H), 6.44 (d, J = 15.6 Hz, 2 H), 7.24−7.32 (m, 12 H), 7.77 (d, J = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 49.0, 123.9, 126.4, 127.3, 127.9, 128.6, 129.7, 134.1, 136.2, 137.5, 143.3; IR (neat) 1187.3, 1138.6 cm^{-1}; LRMS (ESI) *m/z* 404 [$M+H^+$], 421 [$M+NH_4^+$]; HRMS (ESI) calcd for $C_{25}H_{26}NO_2S$ [$M+H^+$]: 404.1679, found: 404.1666.

***N*,*N*-di(4-chlorocinnamyl)-*N*-tosylamine (6b).** The reaction of *p*-toluenesulfonamide (342 mg, 2.0 mmol) with 4-chlorocinnamyl chloride (790 mg, 4.2 mmol), followed by flash chromatography (hexane/$CHCl_3$ 1:3) gave the title compound (400 mg, 42%): TLC R_f 0.28 (hexane/$CHCl_3$ 1:2): ^1H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3 H), 3.98 (d, J = 6.4 Hz, 4 H), 5.97 (dt, J = 6.4, 8.0 Hz, 2 H), 6.38 (d, J = 8.0 Hz, 2 H), 7.16 (d, J = 9.2 Hz, 4 H), 7.25 (d, J = 8.8 Hz, 4 H), 7.31 (d, J = 8.0 Hz, 2 H), 7.75 (d, J = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5,

49.2, 124.7, 127.3, 127.6, 128.8, 129.8, 132.6, 133.6, 134.6, 137.2, 143.5; IR (neat) 3684.0, 3749.6 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{24}NO_2SCl_2$ [M+H^+]: 472.899, found: 472.0896.

Preparation of *N*-cinnamyl-*N*-methyltosylamide (mono-olefinic dialkyl tosylamide derivative). To a round-bottom flask were added cinnamyl bromide (3.72 g, 19.1 mmol), sodium azide (1.6 g, 24.6 mmol) and DMSO (30 mL). Then, the mixture was stirred at room temperature for 9 hours. Water was added, and the mixture was extracted with EtOAc (30 mL x 3), washed with brine (30 mL x 3), dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude mixture of **cinnamylazide**, whose NMR spectra were in agreement with the literature,[24] was used for the next reaction without further purification.

To a round-bottom flask were added cinnamylazide (all amount), triphenylphosphine (8.8 g, 33.6 mmol), water (10 mL) and THF (40 mL), and stirred at room temperature. After 12 hours, dichloroethane was added, and the solution was extracted with 1 N aqueous HCl (30 mL x 3). The residue was basified by 1 M aqueous NaOH to pH 10, then extracted with dichloromethane (30 mL x 3), dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude mixture of **cinnamylamine**, whose NMR spectra were in agreement with the literature,[25] was used for the next reaction without further purification.

To a round-bottom flask were added cinnamylamine (all amount), tosyl chloride (5.0 g, 26.2 mmol) and triethylamine (40 mL), and stirred at room temperature. After 9 hours, water was added, and the mixture was extracted with EtOAc (30 mL x 3), dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was filtered through a short column (2 x 4 cm) of silica gel by using EtOAc as an eluent. After removal of solvent, the solid was washed by EtOAc/hexane to obtain ***N*-tosyl-cinnamylamine** (3.84 g, 70% for 3 steps). The spectra were in agreement with the literature.[26]

To a round-bottom flask were added sodium hydride (120 mg, 2.8 mmol) and DMF (10 mL). The mixture was stirred at 0 ^oC and was added *N*-tosyl-cinnamylamine (280 mg, 0.97 mmol). After 30 minutes, iodomethane (300 mg, 2.1 mmol) was added, and the mixture was stirred at room temperature. After 11 hours, water was added, and the mixture was extracted by EtOAc (20 mL x 3), dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was filtered through a short column (2 x 4 cm) of silica gel by using hexane/EtOAc (1:1) as an eluent to obtain ***N*-cinnamyl-*N*-methyltosylamide** (300 mg, quant); ^1H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 2.72 (s, 3 H), 3.79 (dd, J = 1.2, 6.8 Hz, 2 H), 6.06 (dt, J = 1.2, 15.6 Hz, 1 H), 6.48 (dt, J = 1.2, 15.6 Hz, 1 H), 7.26 (m, 1 H), 7.30−7.35 (m, 6 H), 7.71 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5, 34.3, 52.6, 123.7, 126.4, 127.5, 127.9, 128.6, 129.7, 134.1, 134.5, 136.1, 143.4; IR (neat) 1161.2, 2900.9, 2970.4 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{20}NO_2S$ [M+H^+]: 302.1209, found: 302.1205.

Preparation of (*E*)-diethyl 1-phenyl-1-penten-4,4-dicarboxylate (mono-olefinic dialkyl malonate derivative). To a round-bottom flask were added diethyl 2-methylmalonate (520 mg, 2.99 mmol) and THF (10 mL). At 0 ^{o}C was added *n*-BuLi/THF (1.62 M, 2.0 mL). After stirring for 1 hour at room temperature, cinnamyl bromide (700 mg, 3.55 mmol) was added, and the mixture was stirred at room temperature. After 7 hours, water was added to the reaction mixture, and the resulting solution was extracted by EtOAc (20 mL x 3). The resulting crude mixture was purified with flash chromatography (hexane/EtOAc 20:1 to 5:1) to obtain the title compound (700 mg, 81%): TLC R_f 0.47 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.2 Hz, 6 H), 1.44 (s, 3 H), 2.76 (dd, *J* = 1.6, 7.6 Hz, 2 H), 4.20 (q, *J* = 7.2 Hz, 4 H), 6.10 (dt, *J* = 7.6, 15.6 Hz, 1 H), 6.44 (d, *J* = 16.0 Hz, 1 H), 7.23 (m, 1 H), 7.31 (m, 4 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.1, 20.0, 39.4, 53.8, 61.3, 124.3, 126.2, 127.3, 128.5, 134.0, 137.1, 171.9; HRMS (ESI) calcd for $C_{17}H_{23}O_4$ [M+H$^+$]: 291.1591, found: 291.1582.

Typical procedure for the preparation of carbon-bridged 1,6-dienes (6c–g). To a round-bottom flask was added sodium hydride (3 equiv.) and washed with hexane three times. After removal of hexane by vacuum, DMF, cinnamyl bromide or 4-chlorocinnamyl chloride (2.2 equiv.), and the substrate were added at 0 °C. Then, the mixture was allowed to warm to room temperature and stirred for 4 hours. Water was added to the reaction mixture at 0 ^{o}C, and the solution was extracted with hexane/EtOAc (1:1) and washed with brine. Purification of the crude product by flash chromatography or preparative GPC gave the 1,6-diene starting materials.

(*E*,*E*)-dimethyl 1,7-diphenyl-1,6-heptadien-5,5-dicarboxylate (**6c**) Reaction of dimethyl malonate (1.04 g, 7.87 mmol) with cinnamyl bromide (4.0 g, 20.3 mmol), followed by flash chromatography (hexane/EtOAc 5:1) gave the title compound (1.5 g, 52%): TLC R_f 0.29 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.86 (dd, *J* = 1.2, 7.2 Hz, 4 H), 3.76 (s, 6 H), 6.09 (dt, *J* = 7.2, 15.6 Hz, 2 H), 6.48 (d, *J* = 15.6 Hz, 2 H), 7.23 (m, 2 H), 7.33 (m, 8 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 36.7, 52.5, 58.3, 123.8, 126.2, 127.4, 128.5, 134.2, 137.0, 171.2; IR (neat) 1199.7, 1435.0, 1732.1 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{25}O_4$ [M+H$^+$]: 365.1747, found: 365.1738.

(*E*,*E*)-Dimethyl 1,7-di(4-chlorophenyl)-1,6-heptadien-5,5-dicarboxylate (6d). Reaction of dimethyl malonate (260 mg, 2.0 mmol) with 4-chlorocinnamylchloride (850 mg, 4.6 mmol), followed by flash chromatography (hexane/EtOAc 5:1) and GPC gave the title compound (680 mg, 78%): TLC R_f 0.34 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.82 (dd, *J* = 1.2, 7.6 Hz, 4 H), 3.74 (s, 6 H), 6.04 (dt, *J* = 7.6, 16.0 Hz, 2 H), 6.40 (d, *J* = 13.6 Hz, 2 H), 7.26 (m, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.8, 52.6, 58.1, 124.5, 127.4, 128.7, 133.0, 133.1, 135.4, 171.1; IR (neat) 1211.3, 1292.3, 1728.2 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{22}O_4Cl_2$ [M+H$^+$]: 433.0968,

found: 433.0953.

(*E*,*E*)-Diethyl 1,7-diphenyl-1,6-heptadien-5,5-dicarboxylate (6e). Reaction of diethyl malonate (720 mg, 4.4 mmol) with cinnamyl bromide (2.2 g, 11.2 mmol) followed by flash chromatography (hexane/EtOAc 9:1) and preparative GPC gave the title compound (900 mg, 52%): TLC R_f 0.48 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.2 Hz, 3 H), 1.25 (t, *J* = 7.2 Hz, 3 H), 2.84 (d, *J* = 7.6 Hz, 4 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 6.09 (dt, *J* = 7.6, 15.6 Hz, 1 H), 6.09 (dt, *J* = 7.6, 15.6 Hz, 1 H), 6.47 (d, *J* = 15.6 Hz, 2 H), 7.22–7.34 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 36.6, 57.9, 61.3, 124.0, 126.2, 127.4, 128.5, 134.0, 137.1, 170.8; HRMS (ESI) calcd for $C_{25}H_{28}O_4$ [M+H$^+$]: 393.2060, found: 393.2054.

(*E*,*E*)-Diethyl 1,7-di(4-chlorophenyl)-1,6-heptadien-5,5-dicarboxylate (6f). Reaction of diethyl malonate (370 mg, 2.31 mmol) with 4-chlorocinnamyl chloride (900 mg, 4.81 mmol) followed by flash chromatography (hexane/EtOAc 9:1) and preparative GPC gave the title compound (130 mg, 12%): TLC Rf 0.38 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.2 Hz, 3 H), 1.24 (t, *J* = 7.2 Hz, 3 H), 2.81 (d, *J* = 7.6 Hz, 4 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 6.06 (dt, *J* = 7.2, 14.8 Hz, 2 H), 6.40 (d, *J* = 14.8 Hz, 2 H), 7.25 (m, 8 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2, 36.7, 57.9, 61.4, 124.7, 127.4, 128.7, 132.8, 133.1, 135.5, 170.7; HRMS (ESI) calcd for $C_{25}H_{26}Cl_2O_4$ [M+H$^+$]: 461.1281, found: 461.1273.

9,9-Dicinnamylfluorene (6g). Reaction of fluorene (890 mg, 5.4 mmol) with cinnamyl bromide (2.2 g, 11.2 mmol) followed by preparative GPC separation gave the title compound (1.3 g, 60%): TLC R_f 0.53 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.83 (dd, *J* = 1.2, 7.2 Hz, 4 H), 5.79 (dt, *J* = 7.2, 16.0 Hz, 2 H), 6.22 (d, *J* = 16.0 Hz, 2 H), 7.07 (m, 6 H), 7.15 (m, 4 H), 7.29 (m, 4 H), 7.44 (d, *J* = 8.0 Hz, 2 H), 7.66 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.3, 54.7, 119.9, 123.7, 125.8, 126.0, 126.9, 126.9, 127.2, 128.3, 132.8, 137.4, 140.5, 149.3; HRMS (ESI) calcd for $C_{31}H_{26}$ [M$^+$]: 398.2035, found: 398.2029.

Preparation of *N*-cinnamyl-*N*-((*E*)-4-phenyl-3-buten-1-yl)tosylamide (6h). To a round-bottom flask was added sodium hydride (55% with oil, 310 mg, 7.1 mmol), and washed with dry hexane three times. After removal of hexane by vacuum, were added DMF (15 mL), *N*-cinnamyl-tosylamide (849 mg, 2.96 mmol), and 4-bromo-1-bunene (700 mg, 5.19 mmol), at 0 °C. Then the mixture was stirred for 12 hours at room temperature. Water was added to the reaction mixture, and the resulting solution was extracted by EtOAc (10 mL x 3) and washed with brine (15 mL x 3). The resulting crude product was purified with flash chromatography (hexane/EtOAc 5:1) to obtain ***N*-cinnamyl-*N*-(3-butenyl)tosylamide** (540 mg, 53%): TLC R_f 0.33 (hexane/EtOAc 5:1);

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (q, *J* = 7.2 Hz, 2 H), 2.43 (s, 3 H), 3.24 (dd, *J* = 7.6, 7.6 Hz, 2 H), 3.97 (dd, *J* = 1.2, 6.8 Hz, 2 H), 5.02 (m, 2 H), 5.71 (m, 1 H), 5.97 (dt, *J* = 6.8, 16.0 Hz, 1 H), 6.45 (d, *J* = 15.6 Hz, 1 H), 7.23–7.29 (m, 7 H), 7.73 (d, *J* = 8.4 Hz, 2 H).

To a 10 mL schlenk flask were added *N*-cinnamyl-*N*-(3-butenyl)tosylamide (500 mg, 1.46 mmol), iodobenzene (420 mg, 2.06 mmol), palladium diacetate (43 mg, 0.19 mmol), tri-(*o*-tolyl)phosphine (90 mg, 0.3 mmol), potassium carbonate (400 mg, 2.89 mmol), and DMF (5 mL), and the mixture was stirred for 20 hours at 100 ^{o}C. After cooling to room temperature, the reaction mixture was filtered through a short column (2 × 4 cm) of silica gel by using EtOAc as an eluent. The resulting crude product was purified with flash chromatography (hexane/EtOAc 5:1) to obtain the title compound (150 mg, 25%): TLC R_f 0.32 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3 H), 2.48 (ddt, *J* = 1.2, 7.2, 7.6 Hz, 2 H), 3.30 (dd, *J* = 6.4, 8.0 Hz, 2 H), 3.99 (dd, *J* = 1.2, 6.8 Hz, 2 H), 6.01 (dt, *J* = 6.8, 15.6 Hz, 1 H), 6.07 (dt, *J* = 6.8, 16.0 Hz, 1 H), 6.36, (dd, *J* = 1.2, 16.8 Hz, 1 H), 6.47 (d, *J* 15.6 Hz, 1 H), 7.18–7.29 (m, 12 H), 7.73 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5, 32.5, 47.1, 50.4, 124.4, 126.4, 126.5, 127.2, 127.9, 128.5, 128.6, 129.7, 132.3, 133.7, 136.1, 137.1, 137.2, 143.2; IR (neat) 1153.4, 1319.3, 1446.5 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{27}NO_2S$ [M+H$^+$]: 418.1833, found: 418.1824.

Typical procedure for the oxidation of dienes. In the anodic chamber were placed 0.125 mmol of 1,6-dienes, a supporting electrolyte ($Bu_4NB(C_6F_5)_4$ (460 mg, 0.50 mmol) or Bu_4NBF_4 (490 mg, 0.50 mmol)), DMSO (0.5 mL) and CH_2Cl_2 (4.5 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (30 μL, 0.34 mmol), a supporting electrolyte ($Bu_4NB(C_6F_5)_4$ (460 mg, 0.50 mmol) or Bu_4NBF_4 (490 mg, 0.50 mmol) and CH_2Cl_2 (5 mL). A constant current electrolysis (4.0 mA) was carried out at 0 ^{o}C with magnetic stirring until TLC analysis indicated that the alkene was consumed. Then 0.3 mL of Et_3N was added to both the anodic and the cathodic chambers, and the resulting mixture was heated at 35 ^{o}C with stirring for 1 hour. After removal of the solvent under reduced pressure, the residue was quickly filtered through a short column (2 × 4 cm) of silica gel to remove the supporting electrolyte by using hexane/EtOAc (1:1) containing 1 vol% of triethylamine as an eluent. Purification of the crude products by flash chromatography gave the cyclized carbonyl compounds.

***trans*-3,4-Dibenzoyl-*N*-tosylpyrroridine (8a).** Electrochemical oxidation (2.1 F/mol using $Bu_4NB(C_6F_5)_4$) of *N*,*N*-dicinnamyl-tosylamine (**6a**) (45.6 mg, 0.113 mmol) followed by flash chromatography (hexane/EtOAc 3:1) gave the title compound (36.4 mg, 72%): TLC R_f 0.38 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3 H), 3.40 (m, 2 H), 3.81 (m, 2 H), 4.50 (m, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 7.45 (t, *J* = 7.6 Hz, 4 H), 7.58 (tt, *J* = 1.2, 7.6 Hz, 2 H), 7.66 (d, *J* = 8.0 Hz, 2 H), 7.86 (d, *J* = 8.0 Hz, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 47.1, 50.8, 127.7, 128.6, 128.8, 129.8, 132.7, 133.8, 135.3, 144.0, 197.3; IR (neat) 1342.5, 1674.2

cm^{-1}; LRMS (ESI) *m/z* 434 [M+H^+], 451 [M+NH_4^+]; HRMS (ESI) calcd for $C_{25}H_{24}O_4NS$ [M+H^+]: 434.1421, found 434.1408. The stereochemistry was determined by an X-ray analysis.

X-ray data for *trans*-3,4-Dibenzoyl-*N*-tosylpyrroridine (8a). $C_{25}H_{23}NO_4S$, M = 433.50, monoclinic, space group $P2_1/a$ (No. 14), a = 12.9378(8) Å, b = 8.0214(6) Å, c = 20.4472(11) Å, β = 96.7134(18)°, V = 2107.4(2) $Å^3$, Z = 4, D_c = 1.366 g/cm^3, μ = 1.87 cm^{-1}. Intensity data were measured on a Rigaku RAXIS imaging plate area detector with graphite monochromated Mo-Kα radiation. The data were collected at 100±1 K to maximum 2θ value of 55.0°. A total of 19940 reflections were collected. The structure was solved by SHELX-97[27] and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined by using the riding model. The final cycle of full-matrix least-squares refinement on F^2 was based on 4832 observed reflections ($I > 2.00\sigma(I)$) and 362 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of R = 0.0366 (R_w = 0.0988). All calculations were performed using the Yadokari-XG crystallographic software package.[28]

***trans*-3,4-Di(4-chlorobenzoyl)-*N*-tosyl-pyrrolidine (8b).** Electrochemical oxidation (2.1 F/mol, using $Bu_4NB(C_6F_5)_4$) of *N*,*N*-di-4-chlorocinnamyl-*N*-tosylamine (**6b**) (59.2 mg, 0.125 mmol), followed by flash chromatography (hexane/EtOAc 5:1 with 1 vol% of Et_3N), gave the title compound (56.4 mg, 90%): TLC R_f 0.17 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3 H), 3.36 (m, 2 H), 3.79 (m, 2 H), 4.43 (m, 2 H), 7.34 (d, J = 8.0 Hz, 2 H), 7.44 (dt, J = 2.0, 8.8 Hz, 4 H), 7.66 (d, J = 8.0 Hz, 2 H), 7.81 (d, J = 8.4 Hz, 4 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 47.2, 50.7, 127.7, 129.3, 129.9, 130.0, 132.7, 133.6, 140.6, 144.1, 196.1; IR (neat) 1670.4, 1685.8 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{22}NO_4SCl_2$ [M+H^+]: 502.0641, found: 502.0638.

***trans*-Dimethyl 3,4-dibenzoylcyclopentan-1,1-dicarboxylate (8c).** Electrochemical oxidation (2.1 F/mol) of (*E*,*E*)-dimethyl 1,7-diphenyl-1,6-heptadien-5,5-dicarboxylate (**6c**) (43.8 mg, 0.120 mmol) using Bu_4NBF_4 as a supporting electrolyte at 0 °C, and subsequent treatment with Et_3N followed by flash chromatography (hexane/EtOAc 5:1) gave the title compound (36.9 mg, 78%): TLC R_f 0.39 (hexane/EtOAc 5:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (dd, J = 8.8, 13.6 Hz, 2 H), 3.00 (dd, J = 8.8, 13.6 Hz, 2 H), 3.75 (s, 6 H), 4.52 (m, 2 H), 7.45 (m, 4 H), 7.55 (m, 2 H), 7.98 (d, J = 6.8 Hz, 4 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 38.3, 48.1, 53.0, 60.2, 128.7, 128.7, 133.4, 136.0, 171.3, 199.8; IR (neat) 1207.4, 1249.9, 1678.1, 732.1 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{23}O_6$ [M+H^+]: 395.1489, found: 395.1487. The stereochemistry was determined by the X-ray analysis.

X-ray data for *trans*-Dimethyl 3,4-dibenzoylcyclopentan-1,1-dicarboxylate (8c). $C_{23}H_{22}O_6$ M = 394.41, monoclinic, space group $P2_1/c$ (No. 14), a = 9.4180(5) Å, b = 18.7580(8) Å, c = 11.5320(5) Å, β = 98.9400(14)°, V = 2013(2) Å^3, Z = 4, D_c = 1.302 g/cm^3, μ = 0.94 cm^{-1}. Intensity data were measured on a Rigaku RAXIS imaging plate area detector with graphite monochromated Mo-Kα radiation. The data were collected at 100±1 K to maximum 2θ value of 54.9°. A total of 19514 reflections were collected. The structure was solved by SHELX-97[27] and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined by using the riding model. The final cycle of full-matrix least-squares refinement on F^2 was based on 4595 observed reflections ($I > 2.00\sigma(I)$) and 270 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of R = 0.0455 (R_w = 0.1366). All calculations were performed using the Yadokari-XG crystallographic software package.[28]

***trans*-Dimethyl 3,4-di(4-chlorobenzoyl)cyclopentan-1,1-dicarboxylate (8d).** Electrochemical oxidation (2.1 F/mol) of (*E*,*E*)-dimethyl 1,7-di(4-chlorophenyl)-1,6-heptadien-5,5-dicarboxylate (**6d**) (103.4 mg, 0.239 mmol) using Bu_4NBF_4 as a supporting electrolyte at 0 °C, and subsequent treatment with Et_3N followed by flash chromatography (hexane/EtOAc 4:1) gave the title compound (84.3 mg, 76%): TLC R_f 0.59 (hexane/EtOAc 5:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (dd, J = 8.8, 13.2 Hz, 2 H), 2.96 (dd, J = 8.4, 13.2 Hz, 2 H), 3.74 (s, 6 H), 4.43 (m, 2 H), 7.42 (d, J = 8.8 Hz, 4 H), 7.91 (d, J = 8.8 Hz, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.1, 48.1, 53.1, 60.0, 129.0, 130.1, 134.2, 140.0, 171.2, 198.4; IR (neat) 1091.7, 1678.1, 1732.1 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{21}O_6Cl_2$ [M+H$^+$]: 463.0710, found: 463.0696.

***trans*-Diethyl 3,4-dibenzoylcyclopentane-1,1-dicarboxylate (8e).** Electrochemical oxidation (2.1 F/mol using Bu_4NBF_4) of (*E*,*E*)-diethyl 1,7-diphenyl-1,6-heptadien-5,5-dicarboxylate (**6e**) (48.8 mg, 0.124 mmol) followed by flash chromatography (hexane/EtOAc 5:1) gave the title compound (28.2 mg, 54%): TLC R_f 0.15 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 6 H), 2.33 (dd, J = 9.2, 13.2 Hz, 2 H), 3.01 (dd, J = 8.4, 13.2 Hz, 2 H), 4.20 (t, J = 7.2 Hz, 4 H), 4.20 (m, 2 H), 4.53 (m, 2 H), 7.46 (m, 4 H), 7.55 (t, J = 7.2 Hz, 2 H), 8.00 (d, J = 7.2 Hz, 4 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.0, 38.2, 48.2, 60.2, 61.9, 128.7, 128.7, 133.3, 136.0, 170.9, 200.0; IR (neat) 1246.0, 1678.1, 1728.2 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{27}O_6$ [M+H$^+$]: 423.1802, found: 423.1789.

***trans*-Diethyl 3,4-di(4-chlorobenzoyl)cyclopentane-1,1-di-carboxylate (8f).** Electrochemical oxidation (2.1 F/mol using Bu_4NBF_4) of (*E*,*E*)-diethyl 1,7-di(4-chlorophenyl)-1,6-heptadien-5,5-dicarboxylate (**6f**) (56.6 mg, 0.123 mmol) followed by flash chromatography (hexane/EtOAc 7:1 with 1 vol% of Et_3N) gave the title compound (43.1 mg, 71%): TLC R_f 0.29 (hexane/EtOAc 5:1);

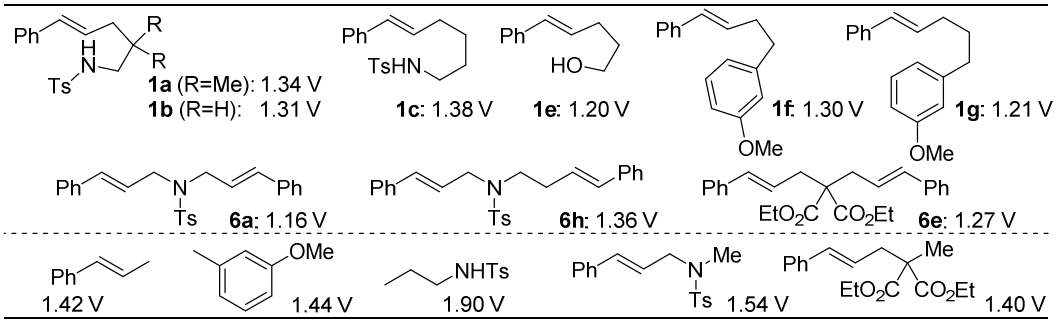
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.2 Hz, 6 H), 2.28 (dd, *J* = 9.2, 13.2 Hz, 2 H), 2.97 (dd, *J* = 8.4, 13.2 Hz, 2 H), 4.20 (m, 4 H), 4.43 (m, 2 H), 7.43 (dd, *J* = 2.0, 6.4 Hz, 4 H), 7.93 (dd, *J* = 2.0, 6.4 Hz, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 38.6, 48.2, 60.1, 62.0, 129.0, 130.1, 134.3, 140.0, 170.8, 198.5; IR (neat) 1246.0, 1678.1, 1728.2 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{25}O_6Cl_2$ [M+H$^+$]: 491.1023, found: 491.1020.

***trans*-3,4-Dibenzoyl-spiro[cyclopentane-1,9'-fluorene] (8g).** Electrochemical oxidation (2.1 F/mol using Bu_4NBF_4) of 9,9-dicinnamylfluorene (**6g**) (99.8 mg, 0.250 mmol) followed by flash chromatography (hexane/EtOAc 5:1) gave the title compound (77.1 mg, 72%): TLC R_f 0.32 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (m, 2 H), 2.72 (m, 2 H), 5.12 (m, 2 H), 7.36 (m, 4 H), 7.45 (m, 4 H), 7.54 (m, 2 H), 7.70 (m, 4 H), 8.07 (d, *J* = 8.4 Hz, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.2, 49.9, 57.8, 119.8, 123.2, 127.4, 128.0, 128.7, 128.8, 133.4, 136.4, 139.4, 152.3, 200.8; HRMS (ESI) calcd for $C_{31}H_{24}O_2$ [M+H$^+$]: 429.1849, found: 429.1847.

***trans*-3,4-Dibenzoyl-*N*-tosyl-piperidine (8h).** Electrochemical oxidation (2.1 F/mol, using $Bu_4NB(C_6F_5)_4$) of *N*-cinnamyl-*N*-((*E*)-4-phenyl-3-buten-1-yl)tosylamide (**6h**) (52.5 mg, 0.125 mmol) followed by flash chromatography (hexane/EtOAc 5:1) gave the title compound (25.2 mg, 45%): TLC R_f 0.54 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80 (dq, *J* = 4.0, 12.8 Hz, 1 H), 2.17 (dd, *J* = 3.2, 13.2 Hz, 1 H), 2.30 (t, *J* = 11.6 Hz, 1H), 2.45 (s, 3 H), 2.46 (m, 1 H), 3.83 (dt, *J* = 3.2, 13.6 Hz, 1 H), 3.99 (d, *J* = 13.6 Hz, 1 H), 4.16 (dd, *J* = 3.6, 11.6 Hz, 1 H), 4.26 (dt, *J* = 3.6, 11.2 Hz, 1 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 7.43 (m, 2 H), 7.55 (m, 3 H), 7.63 (m, 3 H), 7.89 (d, *J* = 8.0 Hz, 2 H), 8.05 (d, *J* = 7.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 28.7, 45.2, 45.5, 46.1, 48.2, 127.6, 128.4, 128.7, 128.7, 128.9, 129.8, 132.7, 133.4, 133.9, 135.3, 144.0, 200.0, 200.9; HRMS (ESI) calcd for $C_{26}H_{26}NO_4$ [M+H$^+$]: 448.1577, found: 448.1580.

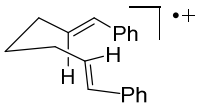
Oxidation potentials. The oxidation potentials of substrates and those of compounds having a partial structure are summarized in Table S1. The oxidation potential of **1d** was not determined in this condition because of a high noise.

Table S1. Oxidation potentials (V vs SCE)



Computational analysis. The optimized structure of the conformers of cation radical of (*E*,*E*)-1,7-diphenyl-1,6-heptadiene, of the *trans*-cyclized cation radical, and of the transition state from the conformer A to the cation radical of *trans*-cyclized cation radical are calculated at UB3LYP/6-31+G(d) level with *C1* symmetry. Cartesian coordinates (Å) are as follows.

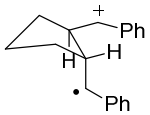
Cartesian coordinates (Å) of Conformer A.



conformer A

Atom	X	Y	Z	Atom	X	Y	Z
C	0.659156	1.616821	-0.74536	H	1.457974	3.343391	-1.79535
C	0.944392	3.150389	-0.84827	H	0.004269	3.711207	-0.88287
C	1.793358	3.560301	0.380129	H	1.204038	4.189399	1.056232
C	2.175095	2.249284	1.07959	H	2.677587	4.139235	0.097359
C	0.969441	1.304314	0.851957	H	3.071233	1.806958	0.625235
C	1.254862	-0.10209	1.105681	H	2.376334	2.373473	2.148622
C	-0.69437	1.240084	-1.13435	H	0.103462	1.666411	1.413753
C	-1.10333	0.10278	-1.86377	H	2.220182	-0.46139	0.745752
C	0.426985	-1.05803	1.732967	H	-1.48918	1.90274	-0.78914
C	0.899859	-2.40134	1.856292	H	1.882794	-2.65047	1.464258
C	0.127834	-3.37559	2.466271	H	0.50254	-4.39075	2.556485
C	-1.14053	-3.04701	2.971509	H	-1.74429	-3.81031	3.454137
C	-1.6296	-1.73468	2.866356	H	-2.60766	-1.48883	3.269332
C	-0.86292	-0.75022	2.263096	H	-1.24634	0.263252	2.208011
C	-0.18915	-0.85795	-2.3933	H	0.879261	-0.72313	-2.2617
C	-0.65336	-1.95894	-3.09599	H	0.050694	-2.68147	-3.4981
C	-2.03084	-2.13577	-3.30342	H	-2.3855	-2.99651	-3.8633
C	-2.95155	-1.20121	-2.80215	H	-4.01485	-1.34074	-2.97237
C	-2.49933	-0.10088	-2.09375	H	-3.20777	0.625605	-1.70358
H	1.417437	1.057509	-1.29915				

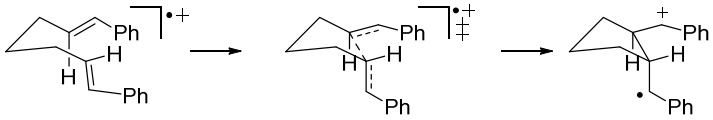
Cartesian coordinates (Å) of the cation radical of *trans*-cyclized cation radical.



Atom	X	Y	Z	Atom	X	Y	Z
C	-2.02898	0.291167	0.586203	H	-3.84807	-0.14017	1.68644

C	-3.58291	0.30794	0.721687	H	-3.97119	1.33172	0.727061
C	-4.13504	-0.5452	-0.42424	H	-4.12934	0.015032	-1.36881
C	-3.1551	-1.71844	-0.49136	H	-5.16599	-0.86739	-0.24668
C	-1.74374	-1.08916	-0.37402	H	-3.32885	-2.40075	0.350581
C	-0.74026	-1.91415	0.278755	H	-3.23277	-2.30545	-1.41218
C	-1.4746	1.433348	-0.12419	H	-1.4155	-0.73104	-1.35177
C	-0.26011	2.114597	0.121311	H	-1.0734	-2.43006	1.180604
C	0.623347	-2.07574	-0.05932	H	-2.04566	1.773397	-0.98946
C	1.444624	-2.87898	0.789485	H	0.997623	-3.35106	1.660685
C	2.791195	-3.05863	0.516403	H	3.402056	-3.67261	1.170307
C	3.362618	-2.44578	-0.60952	H	4.417902	-2.58637	-0.82394
C	2.574962	-1.65955	-1.4672	H	3.024398	-1.19884	-2.34216
C	1.226472	-1.47757	-1.2062	H	0.628855	-0.8763	-1.88406
C	0.611175	1.80061	1.207101	H	0.348017	1.012985	1.906205
C	1.795636	2.497626	1.3821	H	2.452367	2.250701	2.211746
C	2.146478	3.530883	0.497043	H	3.074672	4.076345	0.645172
C	1.301014	3.86921	-0.57083	H	1.573559	4.674372	-1.24697
C	0.117233	3.174155	-0.75912	H	-0.54089	3.431564	-1.58541
H	-1.54702	0.133612	1.551532				

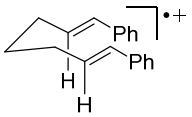
Cartesian coordinates (Å) of the transition state from the conformer A to the cation radical of *trans*-cyclized cation radical.



Atom	X	Y	Z	Atom	X	Y	Z
C	-2.05448	0.220629	0.682371	H	-3.75784	-0.58958	1.71732
C	-3.56549	-0.02143	0.800284	H	-4.09477	0.93352	0.898231
C	-4.0383	-0.82539	-0.41566	H	-4.04739	-0.19885	-1.31754
C	-3.00215	-1.94421	-0.55403	H	-5.05327	-1.21357	-0.28455
C	-1.60826	-1.32808	-0.46589	H	-3.13505	-2.67878	0.250236
C	-0.58703	-2.02127	0.234948	H	-3.09515	-2.4827	-1.5052
C	-1.60983	1.333882	-0.07856	H	-1.29521	-0.8372	-1.38544
C	-0.39464	2.067576	0.059283	H	-0.91447	-2.63097	1.078156
C	0.820086	-1.9888	0.003661	H	-2.26346	1.655606	-0.89073
C	1.669399	-2.69947	0.898214	H	1.226751	-3.23087	1.737178
C	3.043929	-2.72387	0.709258	H	3.67829	-3.27245	1.399049

C	3.610259	-2.04411	-0.37845	H	4.685462	-2.06844	-0.53164
C	2.792427	-1.34188	-1.27863	H	3.237257	-0.82852	-2.12603
C	1.418245	-1.31246	-1.0967	H	0.799238	-0.77877	-1.81067
C	0.550154	1.832146	1.097553	H	0.369241	1.054742	1.832683
C	1.700551	2.600489	1.189457	H	2.411255	2.417024	1.989893
C	1.944092	3.623921	0.258861	H	2.844035	4.226624	0.342384
C	1.025994	3.878087	-0.76981	H	1.214142	4.674498	-1.48358
C	-0.12742	3.113138	-0.86922	H	-0.84416	3.311949	-1.66229
H	-1.49016	0.023243	1.590815				

Cartesian coordinates (Å) of Conformer B.



conformer B

Atom	X	Y	Z	Atom	X	Y	Z
C	4.3505	0.00008	0.252852	H	4.567696	-0.00028	1.328907
C	3.469988	1.207416	-0.11469	H	3.490612	1.36456	-1.20147
C	2.047088	0.78904	0.343284	H	3.789679	2.143479	0.354132
C	2.047275	-0.78933	0.342915	H	1.858015	1.153531	1.35646
C	3.470172	-1.20713	-0.11552	H	1.858522	-1.15432	1.355976
C	0.933052	-1.19296	-0.58946	H	3.790075	-2.1435	0.352554
C	0.93297	1.192812	-0.58915	H	3.490708	-1.36343	-1.20243
C	-0.31472	-1.76808	-0.24835	H	1.187162	-1.20859	-1.64886
C	-1.1805	-2.20094	-1.29773	H	1.187196	1.208506	-1.64852
C	-0.75388	-1.93511	1.097584	H	-0.85792	-2.08423	-2.32944
C	-2.40841	-2.77729	-1.01544	H	-0.11964	-1.62019	1.919568
C	-1.98396	-2.51428	1.369961	H	-3.05254	-3.11139	-1.82322
C	-2.81381	-2.93649	0.319022	H	-2.30484	-2.6463	2.399005
C	-0.3148	1.768002	-0.24814	H	-3.7741	-3.39346	0.540805
C	-1.18043	2.200991	-1.29759	H	-0.85774	2.084318	-2.32927
C	-0.75409	1.934984	1.097758	H	-0.11997	1.61998	1.919795
C	-2.40834	2.777402	-1.0154	H	-3.05235	3.111592	-1.82323
C	-1.98416	2.514218	1.37003	H	-2.30515	2.646202	2.399046
C	-2.81387	2.936545	0.319025	H	-3.77416	3.393563	0.540728
H	5.310118	0.000334	-0.2735				

References

(1) Reviews: (a) Kolb, H. C.; VanNieuwenhze, M. S. Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (b) Jensen, K. H. Sigman, M. S. *Org. Biomol. Chem.* **2008**, *6*, 4083. (c) Cardona, F. Goti, A. *Nat. Chem.* **2009**, *1*, 269.

(2) Recent examples: (a) Zhang, G.; Cui, L.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 1474. (b) Jensen, K. H.; Webb, J. D.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 17471. (c) Asano, K.; Matsubara, S. *J. Am. Chem. Soc.* **2011**, *133*, 16711. (d) de Haro, T.; Nevado, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 906. (e) Souto, J. A.; Martínez, C.; Velilla, I.; Muñiz, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 1. (f) Paderes, M. C.; Belding, L.; Fanovic, B.; Dudding, T.; Keister, J. B.; Chemler, S. R. *Chem.–Eur. J.* **2012**, *18*, 1711.

(3) (a) Harmange, J. C.; Figadere, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711. (b) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504. (c) Elliott, M. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2301. (d) Cole, D. C.; Lennox, W. J.; Lombardi, S.; Ellingboe, J. W.; Bernotas, R. C.; Tawa, G. J.; Mazandarani, H.; Smith, D. L.; Zhang, G.; Coupet, J.; Schechter, L. E. *J. Med. Chem.* **2005**, *48*, 353. (e) Borthwick, A. D. *Res. Rev.* **2005**, *25*, 427.

(4) Recent reviews: (a) Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527. (b) Lund, H. *J. Electrochem. Soc.* **2002**, *149*, S21. (c) Sperry, J. B.; Wright, D. L. *Chem. Soc. Rev.* **2006**, *35*, 605. (d) Yoshida, J.; Kataoka, K.; Horcajada, R.; Nagaki, A. *Chem. Rev.* **2008**, *108*, 2265. (e) Matsumoto, K.; Suga, S.; Yoshida, J. *Org. Biomol. Chem.* **2011**, *9*, 2586.

(5) Recent examples: (a) Hayashi, K.; Kim, S.; Chiba, K. *Electrochemistry* **2006**, *74*, 621. (b) Wu, X.; Dube, M. A.; Fry, A. J. *Tetrahedron Lett.* **2006**, *47*, 7667. (c) Tajima, T.; Kurihara, H.; Fuchigami, T. *J. Am. Chem. Soc.* **2007**, *129*, 6680. (d) Mitsudo, K.; Kaide, T.; Nakamoto, E.; Yoshida, K.; Tanaka, H. *J. Am. Chem. Soc.* **2007**, *129*, 2246. (e) Kakiuchi, F.; Kochi, T.; Mutsutani, H.; Kobayashi, N.; Urano, S.; Sato, M.; Nishiyama, S.; Tanabe, T. *J. Am. Chem. Soc.* **2009**, *131*, 11310. (f) Horii, D.; Fuchigami, T.; Atobe, M. *J. Am. Chem. Soc.* **2007**, *129*, 11692. (g) Zeng, C.-c.; Zhang, N.-t.; Lam, C. M.; Little, R. D. *Org. Lett.* **2012**, *14*, 1314. (h) Kirste, A.; Elsler, B.; Schnakenburg, G.; Waldvogel, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 3571. (i) Finney, E. E.; Ogawa, K. A; Boydston, A. J. *J. Am. Chem. Soc.* **2012**, *134*, 12374. (j) Dai, J.-J.; Huang, Y.-B.; Fang, C.; Guo, Q.-X.; Fu, Y. *ChemSusChem* **2012**, *5*, 617.

(6) Electron-transfer-mediated cyclization reactions: (a) Tokuda, M.; Fujita, H.; Miyamoto, T.; Suginome, H. *Tetrahedron* **1993**, *49*, 2413. (b) Liu, L.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2010**, *49*, 3069.

(7) (a) New, D. G.; Tesfai, Z.; Moeller, K. D. *J. Org. Chem.* **1996**, *61*, 1578. (b) Xu, H.-C.; Moeller, K. D. *J. Am. Chem. Soc.* **2008**, *130*, 13542. (c) Xu, H.-C.; Moeller, K. D. *J. Am.*

Chem. Soc. **2010**, *132*, 2839.

(8) (a) Hudson, C. M.; Marzabadi, M. R.; Moeller, K. D.; New, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 7372. (b) Moeller, K. D.; Tinao, L. V. *J. Am. Chem. Soc.* **1992**, *114*, 1033. (c) Reddy, S. H. K.; Chiba, K.; Sun, Y.; Moeller, K. D. *Tetrahedron* **2001**, *57*, 5183. (d). Huang, Y.-t; Moeller, K. D. *Tetrahedron* **2006**, *62*, 6536.

(9) Schafer, H. J. *Angew. Chem., Int. Ed.* **1981**, *20*, 911.

(10) Ashikari, Y.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2011**, *133*, 11840.

(11) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

(12) Recent reviews: (a) de Meijere, A.; von Zezschwitz, P.; Bräse, S. *Acc. Chem. Res.* **2005**, *38*, 413. (b) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (c) Schmidt, B. *Pure Appl. Chem.* **2006**, *78*, 469. (d) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861. (e) Yoshida, J.; Saito, K.; Nokami, T.; Nagaki, A. *Synlett* **2011**, 1189.

(13) Recent examples: (a) Nagaki, A.; Togai, M.; Suga, S.; Aoki, N.; Mae, K.; Yoshida, J. *J. Am. Chem. Soc.* **2005**, *127*, 11666. (b) Cernak, T. A.; Lambert, T. H. *J. Am. Chem. Soc.* **2009**, *131*, 3124. (c) Wienhofer, I. C.; Studer, A.; Rahman, M. T.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2009**, *11*, 2457. (d) Suga, S.; Yamada, D.; Yoshida, J. *Chem. Lett.* **2010**, *39*, 404. (e) Nagaki, A.; Kenmoku, A.; Moriwaki, Y.; Hayashi, A.; Yoshida, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 7543. (f) Murai, T.; Ohashi, T.; Shibahara, F. *Chem. Lett.* **2011**, *40*, 70. (g) Ohmura, T.; Kijima, A.; Suginome, M. *Org. Lett.* **2011**, *13*, 1238. (h) Nokami, T.; Nozaki, Y.; Saigusa, Y.; Shibuya, A.; Manabe, S.; Ito, Y. Yoshida, J. *Org. Lett.* **2011**, *13*, 1544. (i) Fuchibe, K.; Jyono, H.; Fujiwara, M.; Kudo, T.; Yokota, M.; Ichikawa, J. *Chem.–Eur. J.* **2011**, *17*, 12175. (j) Mitamura, Y.; Yorimitsu, H.; Oshima, K.; Osuka, A. *Chem. Sci.* **2011**, *2*, 2017. (k) Yoshida, M.; Fujino, Y.; Saito, K.; Doi, T. *Tetrahedron* **2011**, *67*, 9993. (l) Amemiya, F.; Matsumoto, H.; Fuse, K.; Kashiwagi, T.; Kuroda, C.; Fuchigami, T.; Atobe, M. *Org. Biomol. Chem.* **2011**, *9*, 4256. (m) Saito, K.; Ueoka, K.; Matsumoto, K.; Suga, S.; Nokami, T.; Yoshida, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 5153. (n) Tomida, Y.; Nagaki, A.; Yoshida, J. *J. Am. Chem. Soc.* **2011**, *133*, 3744. (o) Murata, T.; Murai, M.; Ikeda, Y.; Miki, K.; Ohe, K. *Org. Lett.* **2012**, *14*, 2296. (p) Nagaki, A.; Matsuo, C.; Kim, S.; Saito, K.; Miyazaki, A.; Yoshida, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 3245. (q) Haraguchi, R.; Takada Y.; Matsubara, S. *Chem. Lett.* **2012**, *41*, 628. (r) Kurahashi, K.; Takemoto, Y.; Takasu, K. *ChemSusChem* **2012**, *5*, 270. (s) Fuse, S.; Mifune, Y.; Tanabe, N.; Takahashi, T. *Org. Lett.* **2012**, *10*, 5205.

(14) The oxidation potentials were measured by RDE in $LiClO_4/CH_3CN$ using an SCE as a reference electrode.

(15) Selected examples: (a) Yoshida, J.; Suga, S. *Chem.–Eur. J.* **2002**, *8*, 2651. (b) Yoshida, J.; Suga, S.; Suzuki, S.; Kinomura, N.; Yamamoto, A.; Fujiwara, K. *J. Am. Chem. Soc.* **1999**,

121, 9546. (c) Suga, S.; Suzuki, S.; Yamamoto, A.; Yoshida, J. *J. Am. Chem. Soc.* **2000**, *122*, 10244. (d) Nokami, T.; Ohata, K.; Inoue, M.; Tsuyama, H.; Shibuya, A.; Soga, K.; Okajima, M.; Suga, S.; Yoshida, J. *J. Am. Chem. Soc.* **2008**, *130*, 10864. Radical cation pool, see: (e) Morofuji, T.; Shimizu, A.; Yoshida, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 7259.

(16) ^{1}H NMR study of alkoxysulfonium ions: (a) Garcia, B. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4269. (b) Creary, X.; Burtch, E. A.; Jiang, Z. *J. Org. Chem.* **2003**, *68*, 1117.

(17) The DFT calculations were performed with the Gaussian 09 program: Gaussian 09, Revision A.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, **2009**.

(18) The higher energy barrier from conformer B to the *cis*-cyclized cation radical is also anticipated. However, the transition state of intramolecular cyclization from conformer B to the *cis*-cyclized cation radical could not be determined, although that from conformer A to the *trans*-cyclized cation radical could be determined by DFT calculations.

(19) Lovick, H. M.; Michael, F. E. *J. Am. Chem. Soc.* **2010**, *132*, 1249.

(20) Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002**, *4*, 1471.

(21) Jarboe, S. G.; Beak, P. *Org. Lett.* **2000**, *2*, 357.

(22) Jeong, Y.; Kim, D.-Y.; Choi, Y.; Ryu, J.-S. *Org. Biomol. Chem.* **2011**, *9*, 374.

(23) Gibson, S. E.; Kaufmann, K. A. C.; Haycock, P. R.; White, A. J. P.; Hardick, D. J.; Tozer, M. J. *Organometallics* **2007**, *26*, 1578.

(24) Matsuomoto, K.; Fujie, S.; Ueoka, K.; Suga, S.; Yoshida, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 2506.

(25) Youn, S. W.; Pastline, S. J.; Sames, D. *Org. Lett.* **2004**, *6*, 581.

(26) Kennedy, A. R.; Klett, J.; Mulvey, R. E.; Wright, D. S. *Science* **2009**, *326*, 706.

(27) SHELX 97: G. M. Sheldrick, **1997**.

(28) Yadokari-XG: Kabuto, C.; Akine, S.; Nemoto, T.; Kwon, E. *J. Cryst. Soc. Jpn.* **2009**, *51*, 218.

Chapter 3

Electrochemical Oxidative Hydroxylation *via* Alkoxysulfonium Ions

Abstract

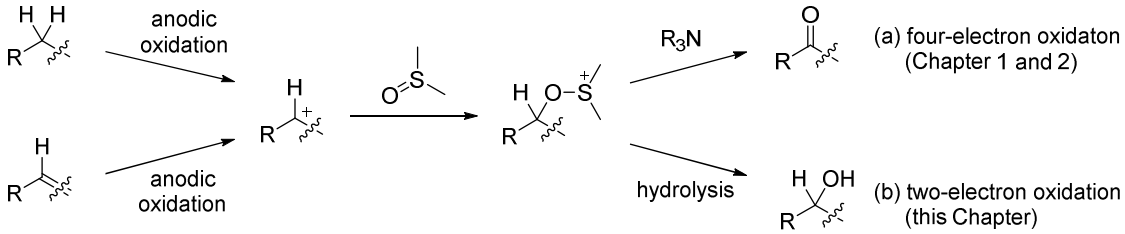
Oxidation of toluene derivatives to benzyl alcohols *via* alkoxysulfonium ion intermediates was achieved by integration of anodic oxidation and hydrolysis, avoiding overoxidation. Alkenes were also oxidized to give 1,2-diols without overoxidation. The integration of electrochemical oxidative cyclization and hydrolysis of alkoxysulfonium ion intermediates was achieved using alkenes bearing a nitrogen atom in an appropriate position to give cyclic β-amino-substituted alcohols

Introduction

Combining multiple steps without isolating intermediates is important to enhance the power and efficiency of organic synthesis.[1,2] The integration of chemical reactions enables synthetic transformations that would be otherwise very difficult or impossible.[3] Oxidation of organic compounds to products that are susceptible to oxidation provides a challenge for organic synthesis. Because products are exposed to the oxidation conditions, significant amounts of undesired overoxidation products are formed during the course of the reaction.[4] Thus, access to a general oxidation method which prevents overoxidation is highly desirable.

Electrochemical reactions using electron transfer on the surface of the electrode serve as a powerful means of selective oxidation.[5,6] Electrochemistry allows for the selective removal of electrons under mild conditions. However, the electrochemical oxidation also often suffers from overoxidation.[7] For example, anodic oxidation of alkenes and that of 1,2-diols often lead to carbon–carbon bond cleavage.[7a,b] As shown in Chapter 1 and 2,[8] alkoxysulfonium ion mediated integrated electrochemical−chemical oxidation based on the "cation pool" method,[9−11] solves the formidable overoxidation problem (Scheme 1a). Electrochemically generated carbocations are converted to the alkoxysulfonium ions, which give the corresponding carbonyl compounds by treatment with amines. It was envisioned that the oxygen–sulfur bond cleavage of the electrochemically generated alkoxysulfonium ions would give the corresponding alcohols (Scheme 1b). Because the oxidation step (electrolysis) and the alcohol-forming step are separated, the products are not exposed to the oxidation conditions, and overoxidation should not occur. This alcohol-forming reaction and previously the reactions giving carbonyl compounds shown in Chapter 1 and 2 are complementary. Herein the aforementioned oxidation reaction *via* electrochemical oxidation to give alkoxysulfonium ions and their hydrolysis are reported.

Scheme 1. Selective Oxidation Mediated by Alkoxysulfonium Ion.

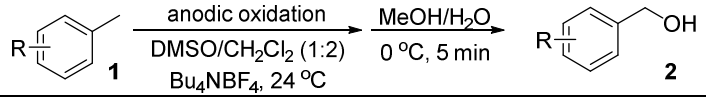


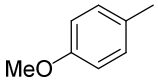
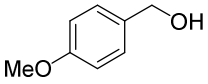
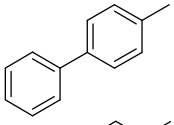
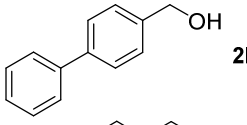
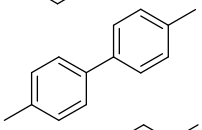
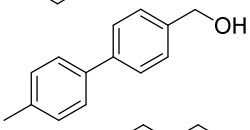
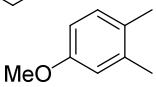
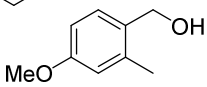
Results and Discussions

First, the oxidation of toluenes to benzyl alcohols was studied.[12] Toluenes **1a** and **1b** were

electrochemically oxidized in the presence of dimethyl sulfoxide (DMSO) in CH_2Cl_2 using Bu_4NBF_4 as a supporting electrolyte at room temperature. A divided cell equipped with a carbon-felt anode and a platinum-plate cathode was used. After electrolysis, the resulting solution was hydrolyzed by aqueous NaOH or $MeOH/H_2O$ at 0 °C to give the corresponding benzyl alcohols **2a** and **2b** in good yields (Table 1).

Table 1. Oxidative Hydrolysis of Toluenes Mediated by Alkoxysulfonium Ions.[a]



entry	toluene		electricity (F/mol)	product		yield (%)[b]
1[c]		**1a**	2.1		**2a**	85
2		**1b**	5.0		**2b**	60
3		**1c**	2.5		**2c**	74
4		**1d**	2.5		**2d**	72

[a]Reactions were carried out on a 0.25 mmol scale. [b]Isolated yield after chromatography. [c]Aqueous NaOH was added instead of $MeOH/H_2O$.

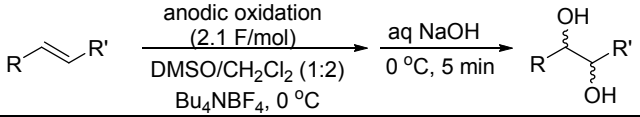
In general, electrochemical benzylic monohydroxylation is quite difficult because the products are also oxidized to give benzaldehyde and benzoic acid.[7c,13] In fact, the oxidation potential of 4-methoxybenzyl alcohol (**2a**) (1.42 V vs SCE) lies close enough to that of 4-methoxytoluene (**1a**) (1.38 V vs SCE)[14] to make selective oxidation of the toluene near impossible. However, the present transformation enables direct oxidation of toluenes to benzyl alcohols with high selectivity. Presumably a positive charge in the alkoxysulfonium ion retards further oxidation by raising the oxidation potential.[15] Alternatively, overoxidation is prevented because a positively charged alkoxysulfonium ion cannot readily approach a positively charged anode.

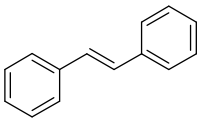
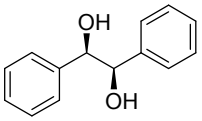
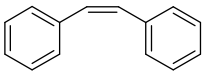
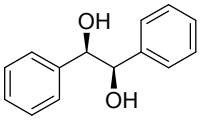
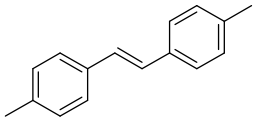
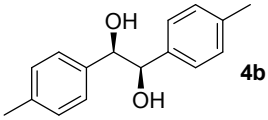
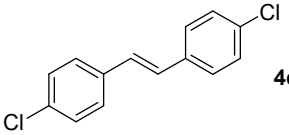
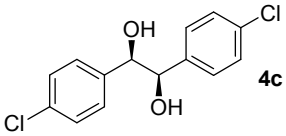
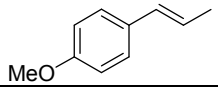
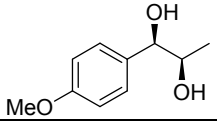
Interestingly, toluenes having more than two methyl groups were selectively oxidized to monoalcohols. Toluene **1c**, which has two methyl groups, was oxidized to monoalcohol **2c** in good yield (Table 1, entry 3). Moreover, *para*-position of methoxy group of toluene **1d** was selectively oxidized to hydroxymethyl group, although there are two different methyl groups (Table 1, entry 4). Prevention of the oxidation of the second methyl group can also be attributed to the positive charge of the alkoxysulfonium ion intermediate.

Next, oxidative dihydroxylation of alkenes was studied.[16] *trans*-Stilbene ((*E*)-**3a**) was

electrochemically oxidized in the presence of DMSO to give the bisalkoxysulfonium ion, whose structure was determined by ^{1}H NMR spectroscopy. Hydrolysis with aqueous NaOH gave the corresponding 1,2-diol **4a**, hydrobenzoin, in 75%yield with high diastereoselectivity (*R***R**/*R***S**=93:7) (Table 2, entry 1). *cis*-Stilbene ((*Z*)-**3a**) gave the same stereoisomer preferentially, although the diastereoselectivity was lower (*R***R**/*R***S**= 66:34) (entry 2).

Table 2. Oxidative Hydrolysis of Alkenes Mediated by Alkoxysulfonium Ions.[a]



entry	alkene	major product	yield (%)[b]	dr[c]
1	 (*E*)-**3a**	 **4a**	75	93:7
2	 (*Z*)-**3a**	 **4a**	69	66:34
3	 **4b**	 **4b**	72	87:13
4	 **4c**	 **4c**	86	91:9
5	 **4d**	 **4d**	52	62:38

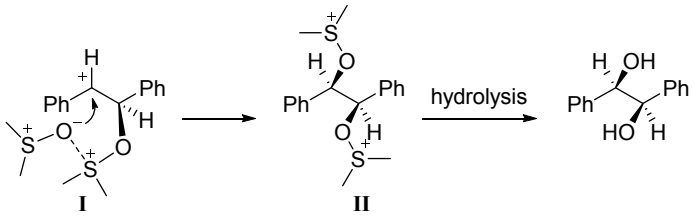
[a]Reactions were carried out on a 0.25 mmol scale. [b]Isolated yield after chromatography. [c]Determined by ^{1}H NMR.

Other stilbene derivatives underwent dihydroxylation under the same conditions with similar diastereoselectivity (entries 3 and 4). A β-methylstyrene derivative **3d** was also oxidized to give the corresponding diol **4d**, although the yield and diastereoselectivity were lower (entry 5). To the best of our knowledge, this is the first example of the direct electrochemical dihydroxylation of alkenes.[17] Although a variety of methods for dihydroxylation of alkenes have been reported, a highly toxic osmium catalyst[18] or explosive peroxides[19] are required in many cases. This present method, however, serves in a mild and environmentally benign manner in the dihydroxylation of alkenes.

Based on the diastereoselectivity observed, a mechanism shown in Scheme 2 was proposed, although the details are not clarified as yet. Presumably intermediate **I** is formed by two-electron oxidation. A conformation in which two phenyl groups are apart is favorable. The sulfonium ion

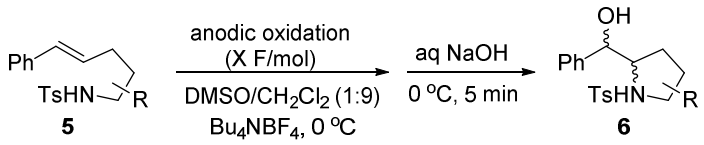
moiety in **I** directs the attack of the second DMSO to give bisalkoxysulfonium ion II,[20] which gives the diol upon hydrolysis.[21]

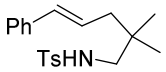
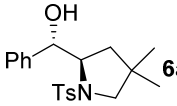
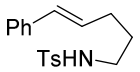
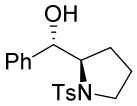
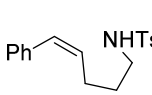
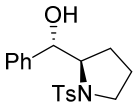
Scheme 2. Proposed Mechanism for Stereoselective Dihydroxylation of Alkenes.



Finally, this present oxidation method was applied to intramolecular alkene cyclization, which assists a powerful synthetic method for the construction of heterocyclic compounds.[22,23] Electrolysis and subsequent hydrolysis of β-alkyl styrenes having a nitrogen nucleophilic moiety in an appropriate position elicited cyclization to give the corresponding alcohols having a pyrrolidine ring in high yields (Table 3). Interestingly, the reaction of (*E*)-isomer of alkene **5a** and **5b** gave the *anti*-addition product selectively (Table 3, entries 1 and 2), although the reaction of the (*Z*)-isomer of alkene **5b** gave a 1:1 mixture (Table 3, entry 3).

Table 3. Oxidative Hydrolysis of Alkenes bearing a Nitrogen Nucleophilic Moiety Mediated by Alkoxysulfonium Ions[a].

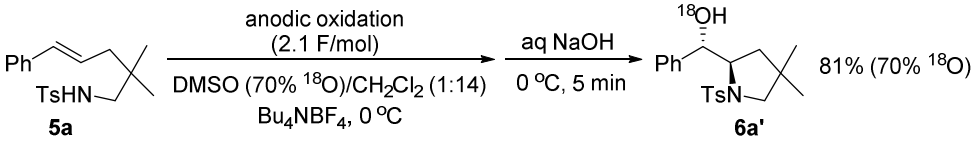


entry	alkene	electricity (F/mol)	major product	yield (%)[b]	dr[c]
1	 **5a**	2.1	 **6a**	79[d]	-[e]
2	 (*E*)-**5b**	2.1	 **6b**	80	90:10
3	 (*Z*)-**5b**	2.5	 **6b**	79	51:49

[a]Reactions were carried out on a 0.13 mmol scale. [b]Isolated yield after chromatography. [c]Determined by ^{1}H NMR. [d]The product was isolated by recrystalization. [e]A small amount of the other diastereomer seemed to be formed as a byproduct, although it was not fully identified.

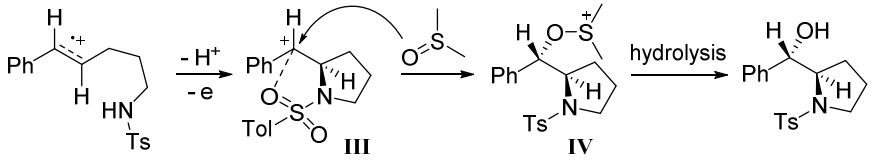
To gain deeper insight into the mechanism, an experiment using ^{18}O-labeled DMSO (containing 70% ^{18}O) was conducted.[24] The product **6a'** containing ^{18}O (70% ^{18}O) was obtained in 81% yield as shown in Scheme 3. It indicates that the oxygen atom of the hydroxyl group in the product is derived from the oxygen atom of DMSO. Therefore, the carbon−oxygen bond in the alkoxysulfonium ion intermediate was not cleaved. Instead, the oxygen−sulfur bond was cleaved upon hydrolysis. This means that the inversion of configuration at the benzylic carbon is not plausible.

Scheme 3. Mechanistic Study Using ^{18}O-DMSO.



A mechanism involving formation of an alkoxysulfonium ion followed by internal S_N2 displacement by the amino group seems to be a reasonable explanation for the stereoselectivity. However, a mechanism involving the cationic intermediate stabilized by the intramolecular interaction with the amino group[25] or the oxygen atom of sulfonyl group seems to be more plausible (Scheme 4), because the oxidation potentials of **5a** and **5b** are lower than those of simple alkyl-substituted styrenes.[26] Thus, the cation radical generated by one-electron oxidation undergoes an intramolecular nucleophilic reaction with a nitrogen atom. After deprotonation, an additional one-electron oxidation takes place to give the benzyl cation intermediate **III** having a conformation in which the benzylic cation center interacts with the amino group as well as the phenyl group and the alkyl chain are apart from each other. The backside attack of DMSO gives the alkoxysulfonium ion intermediate **IV**, which gives the product upon hydrolysis.

Scheme 4. Proposed Mechanism for Stereoselective Cyclization.



Conclusion

In conclusion, a novel oxidative hydroxylation mediated by electrochemically generated alkoxysulfonium ions was developed. Toluenes are oxidized to benzyl alcohols, and alkenes to

1,2-diols stereoselectively. In addition, the method can be applied to intramolecular alkene cyclization to give alcohols bearing a pyrrolidine ring. The intermediacy of alkoxysulfonium ions allows selective oxidation of substrates to alcohols which are easily oxidized under conventional conditions. With the integrated electrochemical–chemical oxidation method described in Chapter 1 and 2, this method provides a novel oxidation system that a reagent for the second step changes the oxidation state of the final products; four-electron oxidation or two-electron oxidation.

Experimental Section

General Remarks. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Varian MERCURY plus-400 (^{1}H 400 MHz, ^{13}C 100 MHz), or JEOL ECA-600P spectrometer (^{1}H 600 MHz, ^{13}C 150 MHz). Chemical shifts are reported using a methine signal of $CHCl_3$ (^{1}H NMR δ 7.26 ppm, ^{13}C NMR δ 77.0 ppm) as an internal standard. Mass spectra were obtained on JEOL JMS SX-102A mass spectrometer. IR spectra were measured with a Shimadzu IRAffinity (FTIR). Merck precoated silica gel F_{254} plates (thickness 0.25 mm) was used for thin-layer chromatography (TLC) analysis. Flash chromatography was carried out on a silica gel (Kanto Chem. Co., Silica Gel N, spherical, neutral, 40–100 mm), or a basic silica gel (Fuji Silysia Chemical LTD., Chromatorex FL-100DX). All oxidation potentials were measured by rotating-disk electrode (RDE) voltammetry using BAS 600C and BAS RRDE-3 rotating disk electrodes, a glassy carbon disk working electrode, a platinum wire counter electrode, and an SCE reference electrode with sweep rate of 10 mVs^{-1} at 3000 rpm in 0.1 M $LiClO_4/CH_3CN$. X-ray single crystal structure analysis was performed on RIGAKU R-AXIS RAPID. All reactions were carried out under argon atmosphere unless otherwise noted. The anodic oxidation was carried out using an H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon JF-20-P7, ca. 160 mg for 0.25 mmol scale or ca. 80 mg for 0.13 mmol scale, dried at 300 ^{o}C/1 mmHg for 4 hours before use) and a platinum plate cathode (10 mm x 10 mm).

Materials. Bu_4NBF_4 was purchased from TCI and dried at 50 ^{o}C/1 mmHg overnight. Dichloromethane was washed with water, distilled from P_2O_5, redistilled from dried K_2CO_3 to remove a trace amount of acid, and stored over molecular sieves 4A. Anhydrous-dimethyl sulfoxide (DMSO) was purchased from Aldrich, and stored over molecular sieves 4A. Ethyl acetate was purchased from TCI, washed with saturated aqueous sodium hydrogen carbonate, with brine, distilled from P_2O_5, and stored over molecular sieves 4A. ^{18}O-labeled DMSO was prepared according to the reported procedures.[24] Compounds **5a** and **5b** were prepared according to the reported procedures.[27] Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification.

Oxidation of 4-methoxytoluene (1a); a typical procedure for oxidation of toluene derivatives. In the anodic chamber were placed 4-methoxytoluene (**1a**) (30.2 mg, 0.247 mmol), Bu_4NBF_4 (350 mg, 1.06 mmol), DMSO (3.6 mL), and 0.3 M Bu_4NBF_4/CH_2Cl_2 (6.4 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (55 μL, 0.62 mmol) and 0.3 M Bu_4NBF_4/CH_2Cl_2 (10 mL). The constant current electrolysis (8.0 mA) was carried out at 24 ^{o}C with magnetic stirring until TLC analysis indicated the complete consumption of the starting material (2.1 F/mol of electricity was consumed). Then the anodic solution was cooled at 0 ^{o}C, and aqueous NaOH (1 N, 1.0 mL) was added to the both anodic and cathodic chambers. The

resulting mixture was stirred for additional 5 minutes, and Et_3N (1.0 mL) was added to the both chambers as a quenching agent. The solution was poured into water (20 mL), and the mixture was extracted with Et_2O (20 mL x 3). The extracts were dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was quickly filtered through a short column (2 x 4 cm) of silica gel to remove Bu_4NBF_4 by using Et_2O as an eluent. Purification of the crude product by flash chromatography (hexane/EtOAc 3:1) gave **4-methoxybenzyl alcohol** (**2a**) (29.0 mg, 85%): TLC R_f 0.14 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.54 (s, 3 H), 4.30 (s, 2 H), 6.61 (d, J = 8.8 Hz, 2 H), 7.03 (d, J = 8.4 Hz, 2 H). The ^{1}H NMR spectrum was matched with that of a compound purchased from a commercially source.

4-Phenylbenzyl alcohol (**2b**)**.** Electrochemical oxidation (5.0 F/mol) of 4-methylbiphenyl (**1b**) (42.2 mg, 0.251 mmol) and subsequent treatment with MeOH/H_2O (1:1) followed by flash chromatography (hexane/EtOAc 3:1) gave the title compound (27.5 mg, 60%): TLC R_f 0.06 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80 (s, 1 H), 4.74 (s, 2 H), 7.36 (m, 1 H), 7.45 (m, 4 H), 7.60 (d, J = 7.2 Hz, 2 H). The spectra were in agreement with the literature.[28]

4-(4-Tolyl)benzyl alcohol (2c). Electrochemical oxidation (2.5 F/mol) of 4,4'-dimethylbiphenyl (**1c**) (45.7 mg, 0.251 mmol) and subsequent treatment with MeOH/H_2O (1:1) followed by flash chromatography (hexane/EtOAc 3:1) gave the title compound (37.0 mg, 74%): TLC R_f 0.14 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85 (s, 1 H), 2.42 (s, 3 H), 4.74 (s, 2 H), 7.27 (d, J = 8.0 Hz, 2 H), 7.43 (d, J = 8.0 Hz, 2 H), 7.51 (d, J = 8.0 Hz, 2 H), 7.59 (dd, J = 1.6, 6.4 Hz, 2 H). The spectra were in agreement with the literature.[29]

2-Methyl-4-methoxybenzyl alcohol (2d). Electrochemical oxidation (2.5 F/mol) of 1-methoxy-3,4-dimethylbenzene (**1d**) (34.0 mg, 0.250 mmol) and subsequent treatment with MeOH/H_2O (1:1) followed by flash chromatography (hexane/EtOAc 3:1) gave the title compound (27.4 mg, 72%): TLC R_f 0.09 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3 H), 3.79 (s, 3 H), 4.63 (s, 2 H), 6.73 (m, 2 H), 7.23 (d, J = 8.0 Hz, 1 H). The spectra were in agreement with the literature.[30]

Oxidation of *trans*-stilbene (3a): a typical procedure for oxidation of aryl-substituted alkenes. In the anodic chamber were placed *trans*-stilbene (**3a**) (46.5 mg, 0.258 mmol), Bu_4NBF_4 (350 mg, 1.06 mmol), DMSO (3.6 mL) and 0.3 M Bu_4NBF_4/CH_2Cl_2 (6.4 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (60 μL, 0.68 mmol) and 0.3 M Bu_4NBF_4/CH_2Cl_2 (10 mL). The constant current electrolysis (8.0 mA) was carried out at 0 ^oC with magnetic stirring until TLC analysis indicated that the starting material was consumed (2.1 F/mol of electricity). Then 1 mL of 1 N aqueous NaOH was added to both the anodic and the

cathodic chambers, and the resulting mixture was stirred for 5 minutes. The anodic solution was poured into water (20 mL), and the mixture was extracted with Et_2O (20 mL x 3). The extracts were dried over Na_2SO_4. After removal of solvent under reduced pressure, the residue was quickly filtered through a short column (2 x 4 cm) of basic silica gel to remove Bu_4NBF_4 using hexane/EtOAc (1:1) as an eluent. Purification of the crude product by flash chromatography (hexane/EtOAc 3:1) gave a diastereo mixture of **1,2-diphenylethane-1,2-diol** (**4a**) (41.5 mg, 75%) in 93:7 selectivity which was determined by ^{1}H NMR analysis. **(1*R**,2*R**)-1,2-Diphenylethane-1,2-diol**: TLC R_f 0.58 (hexane/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.91 (s, 2 H), 4.70 (s, 2 H), 7.12 (m, 4 H). **(1*R**,2*S**)-1,2-Diphenylethane-1,2-diol**: TLC R_f 0.58 (hexane/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 2 H), 4.84 (s, 2 H), 7.28 (m, 10 H).7.33 (m, 6 H). The spectra were in agreement with those of compounds purchased from a commercialy source.

1,2-Di(*p*-methylphenyl)ethane-1,2-diol (4b). Electrochemical oxidation (2.1 F/mol) of 4,4'-dimethyl-*trans*-stilbene (**3b**) (51.6 mg, 0.248 mmol) and subsequent treatment with 1 N aqueous NaOH followed by flash chromatography (hexane/EtOAC 3:1) gave the title compound (43.3 mg, 72%) as a mixture of diastereomers (86:14), which were identified as a mixture by ^{1}H NMR. Major isomer (*R**,*R**): TLC R_f 0.64 (hexane/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 6 H), 2.84 (s, 2 H), 4.66 (s, 2 H), 7.04 (m, 8 H). Minor isomer (*R**,*S**): TLC R_f 0.64 (hexane/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 6H), 4.73 (s, 2 H), 6.99-7.14 (m, 8 H). The spectra were in agreement with the literature.[31]

1,2-Di(4-chlorophenyl)ethane-1,2-diol (4c). Electrochemical oxidation (2.1 F/mol) of 4,4'-dichloro-*trans*-stilbene (**3c**) (63.0 mg, 0.253 mmol) and subsequent treatment with 1 N aqueous NaOH followed by flash chromatography (hexane/EtOAc 3:1) gave the title compound (61.5 mg, 86%) as a mixture of diastereomers (91:9), which were identified as a mixture by ^{1}H NMR. Major isomer (*R**,*R**): TLC R_f 0.59 (hexane/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.02 (s, 2 H), 4.58 (s, 2 H), 7.00 (d, J = 8.4 Hz, 4 H), 7.20 (d, J = 8.8 Hz, 4 H). Minor isomer (*R**,*S**): TLC R_f 0.59 (hexane/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 2 H), 4.80 (s, 2 H), 7.08 (d, J = 8.8 Hz, 4 H), 7.25 (d, J = 8.8 Hz, 4 H). The spectra were in agreement with the literatures (major isomer[32], minor isomer[33]).

1-(4-Methoxyphenyl)propane-1,2-diol (4d). Electrochemical oxidation (2.5 F/mol) of (*E*)-1-(4-methoxyphenyl)propene (**3d**) (37.4 mg, 0.250 mmol) and subsequent treatment with 1 N aqueous NaOH followed by flash chromatography (hexane/EtOAc 2:1) gave the title compound (23.7 mg, 52%) as a mixture of diastereomers (62:38) selectivity, which were identified by ^{1}H NMR (400 MHz, $CDCl_3$). Major isomer (*R**,*R**): TLC R_f 0.27 (hexane/EtOAc 1:1); ^{1}H NMR δ

1.02 (d, J = 6.4 Hz, 3 H), 3.80 (s, 3 H), 3.82 (m, 1 H), 4.31 (d, J = 7.6 Hz, 1 H), 6.88 (d, J = 8.8 Hz, 2 H), 7.25 (d, J = 8.4 Hz, 2 H); Minor isomer (*R**,*S**): TLC R_f 0.27 (hexane/EtOAc 1:1); ^{1}H NMR δ 1.08 (d, J = 6.4 Hz, 3 H), 3.80 (s, 3 H), 3.98 (m, 1 H), 4.59 (d, J = 4.8 Hz, 1 H), 6.89 (d, J = 8.8 Hz, 2 H), 7.27 (d, J = 8.4 Hz, 2 H). The spectra were in agreement with the literatures (major isomer[34], minor isomer[35]).

Preparation of (*Z*)-*N*-tosyl-5-phenyl-4-pentenamine ((*Z*)-5b). To a round-bottom flask were added phenylacethylene (1.1 mL, 10 mmol), 1-bromo-3-chloropropane (1.5 mL, 14 mmol), and THF (40 mL). The solution was cooled to −78 ^{o}C. A solution of *n*-butyllithium in hexane (1.62 M, 7.4 mL, 12 mmol) was slowly added and the mixture was heated to 80 ^{o}C (reflux). After 15 hours, the complete consumption of phenylacethylene was indicated by ^{1}H NMR analysis, and the solution was cooled at 0 ^{o}C. Aqueous NH_4Cl was added and the solution was extracted with EtOAc (20 mL x 3), washed with brine (20 mL x 3), dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified with flash chromatography (hexane) to obtain **1-phenyl-5-chloro-1-pentyne** (1.64 g, 92%): TLC R_f 0.27 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.07 (tt, J = 6.8, 6.8 Hz, 2 H), 2.62 (t, J = 6.8 Hz, 2 H), 3.72 (t, J = 6.4 Hz, 2 H), 7.28 (m, 3 H), 7.41 (m, 2 H). The spectra were in agreement with the literature.[36]

To a round-bottom flask were added 1-phenyl-5-chloro-1-pentyne (520 mg, 2.91 mmol), palladium-calcium carbonate poisoned with lead (Lindlar's catalyst) (900 mg, ca. 0.45 mmol), quinoline (1.06 mL, 9.03 mmol). The flask was flashed by H_2 (balloon), then EtOAc (distilled, 30 mL) was added, and the solution was stirred at room temperature. After 11 hours, quinoline (1.0 mL) was additionally added. After additional 24 hours, Lindlar's catalyst (900 mg) was additionally added. After additional 11 hours, the ^{1}H NMR analysis indicated the complete consumption of the alkyne. Then, the mixture was filtrated through celite to remove catalyst. The filtrate was filrated through a short column (2 x 4 cm) of silica gel to remove quinoline using hexane as an eluent, and to obtain **(*Z*)-1-phenyl-5-chloro-1-pentene** (250 mg, 48%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (m, 2 H), 2.49 (q, J = 7.6 Hz, 2 H), 3.56 (t, J = 6.4 Hz, 2 H), 5.63 (dt, J = 7.6, 11.6 Hz, 1 H), 6.48 (d, J = 11.6 Hz, 1 H), 7.26 (m, 3 H), 7.35 (m, 2 H). The spectra were in agreement with the literature.[36]

To a round-bottom flask were added (*Z*)-1-phenyl-5-chloro-1-pentene (250 mg, 1.4 mmol), sodium iodide (310 mg, 2.1 mmol), and acetone (10 mL), and the solution was heated at 60 ^{o}C (reflux). After 14 hours, the mixture was cooled to room temperature, was added water, was extracted with ethyl acetate (10 mL x 3), was dried over Na_2SO_4, and the solvent was removed under reduced pressure. After filtration through a short column (2 x 4 cm) of silica gel using hexane as an eluent, the crude product containing **(*Z*)-1-phenyl-5-iodo-1-pentene** (400 mg) was used for next reaction without additional purification. To a round-bottom flask were added (*Z*)-1-phenyl-5-iodo-1-pentene (400 mg, 1.4 mmol), cesium carbonate (520 mg, 1.6 mmol),

p-toluenesulfonamide (277 mg, 1.6 mmol), and DMF (10 mL), and the solution was heated at 60 ^{o}C. After 14 hours, the solution was cooled at room temperature, and water was added. The mixture was extracted with ethyl acetate (10 mL x 3). The extracts were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified with flash chromatography (hexane/EtOAc 4:1) to obtain **(*Z*)-*N*-tosyl-5-phenyl-4-pentenamine** (**(*Z*)-5b**) (400 mg, 86%): TLC R_f 0.17 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (m, 2 H), 2.31 (dq, *J* = 1.6 , 7.6 Hz, 2H), 2.95 (q, *J* = 6.8 Hz, 2 H), 4.30 (m, 1 H), 5.54 (dt, *J* = 7.2, 11.6 Hz, 1 H), 6.43 (d, *J* = 11.6 Hz, 1 H), 7.19−7.33 (m, 7 H), 7.70 (dt, *J* = 1.6, 8.0 Hz, 2 H). The spectra were in agreement with the literature.[37]

Oxidation of (*E*)-*N*-tosyl-2,2-dimethyl-5-phenyl-4-pentenamine (5a): a typical procedure for oxidation of alkenes bearing a nucleophilic functional group. In the anodic chamber were placed (*E*)-*N*-tosyl-2,2-dimthyl-5-phenyl-4-pentenamine (**5a**) (43.6 mg, 0.127 mmol), Bu_4NBF_4 (180 mg, 1.5 mmol), DMSO (0.5 mL) and CH_2Cl_2 (4.5 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (25 μL, 0.3 mmol), Bu_4NBF_4 (180 mg, 1.5 mmol), and CH_2Cl_2 (5 mL). The constant current electrolysis (4.0 mA) was carried out at 0 ^{o}C with magnetic stirring until TLC analysis indicated that the starting material was consumed (2.1 F/mol of electricity). Then 0.5 mL of 1 N aqueous NaOH was added to both the anodic and the cathodic chambers, and the resulting mixture was stirred for 5 minutes at 0 ^{o}C. The mixture was poured into water, extracted with diethyl ether (10 mL x 3), and dried over Na_2SO_4. After removal of solvent under reduced pressure, the residue was quickly filtered through a short column (2 x 4 cm) of silica gel to remove Bu_4NBF_4 using hexane/EtOAc (1:1) as an eluent. Purification of the crude product by flash chromatography (hexane/EtOAc 4:1) gave **(*S**)-phenyl((*R**)-*N*-tosyl-4,4-dimethylpyrrolidin-2-yl)methanol** (**6a**) (41.1 mg, 90%), which might contain a small amount of (*R**)-phenyl((*R**)-*N*-tosyl-4,4-dimethylpyrrolidin-2-yl)methanol, although it was not fully characterized. The product was recrystalized from hexane to obtain pure **6a** (36.1 mg, 79%): TLC R_f 0.10 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.32 (s, 3 H), 0.95 (s, 3 H), 1.04 (dd, *J* = 6.8, 12.4 Hz, 1 H), 1.88 (dd, *J* = 10.4, 10.4 Hz, 1 H), 2.44 (s, 3 H), 2.70 (d, *J* = 3.2 Hz, 1 H), 3.16 (d, *J* = 11.2 Hz, 1 H), 3.28 (d, *J* = 10.8 Hz, 1 H), 5.48 (m, 1 H), 7.26 (m, 1 H), 7.36 (m, 6 H), 7.81 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 25.6, 25.9, 36.9, 38.7, 62.5, 66.1, 72.7, 125.7, 127.3, 127.5, 128.2, 129.8, 135.0, 140.2, 143.8; HRMS (ESI) calcd for $C_{20}H_{25}O_3NS$ [M+H$^+$]: 360.1628, found 360.1623. The stereochemistry was determined by the X-ray analysis.

X-ray data for (*S)-phenyl((*R**)-*N*-tosyl-4,4-dimethylpyrrolidin-2-yl)methanol (6a).** $C_{20}H_{25}N_3O_4S$, *M* = 359.47, monoclinic, space group $P2_1/a$ (No. 14), *a* = 11.6681(6) Å, *b* = 13.4566(6) Å, *c* = 12.2485(5) β = 98.5655(14)^{o}, *V* = 1901.72(15) Å^3, *Z* = 4, D_c = 1.256 g/cm^3, μ = 1.88 cm^{-1}. Intensity data were measured on a Rigaku RAXIS imaging plate area detector with

graphite monochromated Mo-Kα radiation. The data were collected at 100±2 K to maximum 2θ value of 55.0°. A total of 17928 reflections were collected. The structure was solved by SHELX-97[38] and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined by using the riding model. The final cycle of full-matrix least-squares refinement on F^2 was based on 4341 observed reflections ($I > 2.00\sigma(I)$) and 326 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of $R = 0.0378$ ($R_w = 0.1060$). All calculations were performed using the Yadokari-XG crystallographic software package.[39] The CCDC number is 859629.

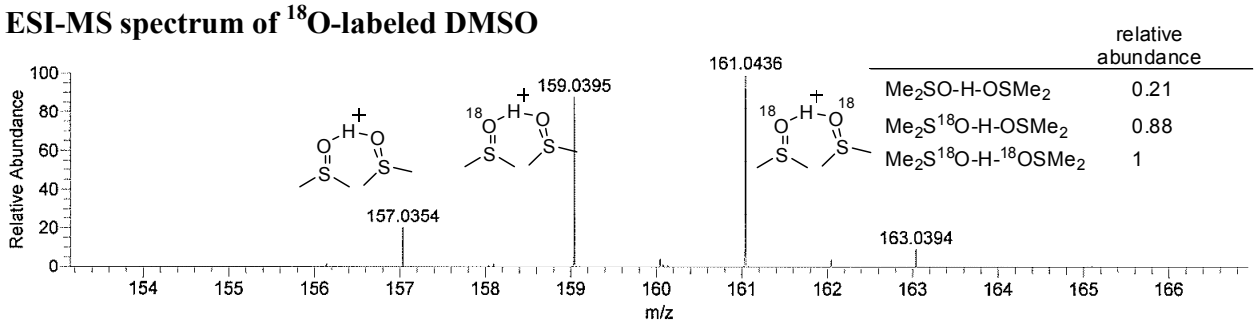
Phenyl(*N*-tosyl-pyrrolidin-2-yl)methanol (6b). Electrochemical oxidation (2.1 F/mol) of (*E*)-*N*-tosyl-5-phenyl-4-pentenamine (**(*E*)-5b**) (40.6 mg, 0.129 mmol) in DMSO/CH_2Cl_2 (1:9) and subsequent treatment with 1 N aqueous NaOH followed by flash chromatography (hexane/EtOAc 3:1) gave the title compound as diastereomixtures (90:10) (34.3 mg, 80%). **(*S**)-Phenyl((*R**)-*N*- tosyl-pyrrolidin-2-yl)methanol**: TLC R_f 0.65 (hexane/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 118-1.28 (m, 2 H), 1.59 (m, 1 H), 1.83 (m, 1 H), 2.44 (s, 3 H), 3.07 (d, J = 4.0 Hz, 1 H), 3.24-3.38 (m, 2 H), 3.80 (m, 1 H), 5.24 (m, 1 H), 7.26 (m, 2 H), 7.33 (m, 3 H), 7.41 (m, 2 H), 7.77 (d, J = 6.8 Hz, 2 H). **(*R**)-Phenyl((*R**)-*N*-tosyl-pyrrolidin-2-yl)methanol**: TLC R_f 0.65 (hexane/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (m, 1 H), 1.35 (m, 1 H), 1.50 (m, 1 H), 1.57 (s, 1 H), 2.43 (s, 3 H), 3.27 (m, 1 H), 3.40 (m, 1 H), 3.81 (dt, J = 2.8, 8.0 Hz, 1 H), 3.84 (d, J = 2.0 Hz, 1 H), 4.64 (dd, J = 2.0, 8.0 Hz, 1 H), 7.32 (m, 5 H), 7.41 (m, 2 H), 7.78 (d, J = 8.0 Hz, 2 H). The spectra of both isomers were in agreement with the literature.[40]

The case of oxidation of (*Z*)-isomer of starting material (*Z*)-5b. Electrochemical oxidation (2.5 F/mol) of (*Z*)-*N*-tosyl-5-phenyl-4-pentenamine (**(*Z*)-5b**) (39.7 mg, 0.126 mmol) and subsequent treatment with 1 N aqueous NaOH followed by flash chromatography (hexane/EtOAc 5:1) gave the title compound (32.9 mg, 79%) as a mixture of diastereomers (*S***R**/*R***R** = 51:49).

^{18}O-labeled (*S)-phenyl((*R**)-*N*-tosyl-4,4-dimethylpyrrolidin-2-yl)methanol (6a').** In the anodic chamber were placed (*E*)-*N*-tosyl-2,2-dimthyl-5-phenyl-4-pentenamine (**5a**) (42.3 mg, 0.123 mmol), Bu_4NBF_4 (490 mg, 1.5 mmol), ^{18}O-labeled DMSO (70% of ^{18}O containing, 0.35 mL) and CH_2Cl_2 (4.65 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (25 μL, 0.62 mmol), Bu_4NBF_4 (490 mg, 1.5 mmol) and CH_2Cl_2 (5 mL). The constant current electrolysis (4.0 mA) was carried out at 0 °C with magnetic stirring until 2.1 F/mol of electricity was consumed. Then 0.5 mL of 1 N aqueous NaOH was added to both the anodic and the cathodic chambers, and the resulting mixture was stirred for 5 minutes at 0 °C. The mixture was poured into water, extracted with diethyl ether (10 mL x 3), and dried over Na_2SO_4. After removal of solvent of anodic solution under reduced pressure, the residue was quickly filtered

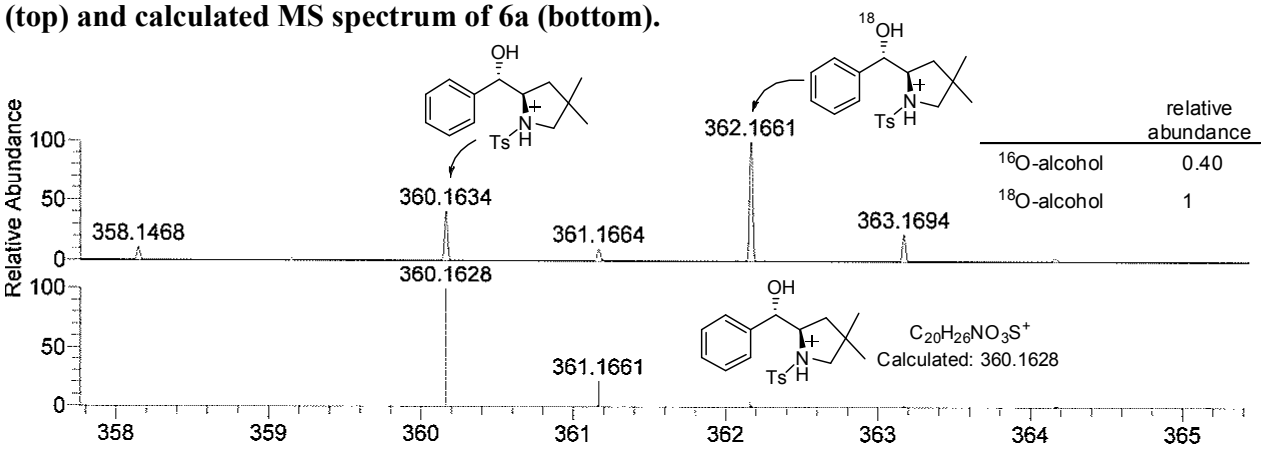
through a short column (2 x 4 cm) of silica gel to remove Bu_4NBF_4 using hexane/EtOAc (1:1) as an eluent. Purification of the crude product by flash chromatography (hexane/EtOAc 4:1) and recrystalization (hexane/EtOAc) gave the title compound (36.1 mg, 81%) containing 70% of ^{18}O at hydroxyl group: TLC R_f 0.15 (hexane/EtOAc 5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 0.31 (s, 3 H), 0.95 (s, 3 H), 1.04 (dd, *J* = 7.2, 12.4 Hz, 1 H), 1.88 (dd, *J* = 10.4, 12.4 Hz, 1 H), 2.44 (s, 3 H), 2.76 (d, *J* = 3.2 Hz, 1 H), 3.16 (d, *J* = 10.8 Hz, 1 H), 3.27 (d, *J* = 10.8 Hz, 1 H), 3.81 (m, 1 H), 5.48 (s, 1 H), 7.26 (m, 2 H), 7.35 (m, 5 H), 7.81 (d, *J* = 7.6 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 25.6, 25.9 36.9, 38.7, 62.4, 66.1, 72.7 (two peaks were detected indicating benzylic carbon connecting to ^{16}O and ^{18}O respectively), 125.7, 127.2, 127.4, 128.2, 129.8, 135.0, 140.2, 143.8. The molecule weight was determined by ESI-MS (*vide infra*).

ESI-MS spectrum of ^{18}O-labeled DMSO



The ESI-MS spectrum indicates that the ratio of DMSO/DMSO-^{18}O is 31:69.

ESI-MS spectrum of ^{18}O-labeled (*N*-tosyl-4,4-dimethylpyrrolidin-2-yl)phenylmethanol (6a') (top) and calculated MS spectrum of 6a (bottom).



The ESI-MS spectrum indicates that the ratio of $^{16}O/^{18}O$ of (*N*-tosyl-4,4-dimethylpyrrolidin-2-yl)phenylmethanol (**6a**/**6a'**) generated from ^{18}O-labeled DMSO is 29:71.

References

(1) For reviews, see: (a) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177. (b) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195. (c) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312. (d) Ugi, I. *Pure Appl. Chem.* **2001**, *73*, 187. (e) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365. (f) de Meijere, A.; von Zezschwitz, P.; Bräse, S. *Acc. Chem. Res.* **2005**, *38*, 413. (g) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (h) Schmidt, B. *Pure Appl. Chem.* **2006**, *78*, 469. (i) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861.

(2) For recent examples, see: (a) Shimizu, M.; Shimono, K.; Hiyama, T. *Chem. Lett.* **2006**, *35*, 838. (b) Clarke, P. A.; Santos, S.; Martin, W. H. C. *Green Chem.* **2007**, *9*, 438. (c) Bremner, W. S.; Organ, M. G. *J. Comb. Chem.* **2007**, *9*, 14. (d) Fuwa, H.; Tako, T.; Ebine, M.; Sasaki, M. *Chem. Lett.* **2008**, *37*, 904. (e) Nokami, T.; Tsuyama, H.; Shibuya, A.; Nakatsutsumi, T.; Yoshida, J. *Chem. Lett.* **2008**, *37*, 942. (f) Ikeda, S.; Shibuya, M.; Kanoh, N.; Iwabuchi, Y. *Chem. Lett.* **2008**, *37*, 962. (g) Numata, Y.; Kawashima, J.; Hara, T.; Tajima, Y. *Chem. Lett.* **2008**, *37*, 1018. (h) Yamaguchi, K.; Kotani, M.; Kamata, K.; Mizuno, N. *Chem. Lett.* **2008**, *37*, 1258. (i) Babu, G.; Orita, A.; Otera, J. *Chem. Lett.* **2008**, *37*, 1296. (j) Cernak, T. A.; Lambert, T. H. *J. Am. Chem. Soc.* **2009**, *131*, 3124. (k) Hardee, D. J.; Lambert, T. H. *J. Am. Chem. Soc.* **2009**, *131*, 7536.

(3) (a) Suga, S.; Yamada, D.; Yoshida, J. *Chem. Lett.* **2010**, *39*, 404. (b) Yoshida, J.; Saito, K.; Nokami, T.; Nagaki, A. *Synlett* **2011**, 1189.

(4) (a) Muzart, J.; Aït-Mohand, S. *Tetrahedron Lett.* **1995**, *36*, 5735. (b) Li, F.; Wang, M.; Ma, C.; Gao, A.; Chen, H.; Sun, L. *Dalton Trans.* **2006**, *35*, 2427. (c) Nagataki, T.; Itoh, S. *Chem. Lett.* **2007**, *36*, 748.

(5) Recent reviews on organic electrochemistry: (a) Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527. (b) Lund, H. *J. Electrochem. Soc.* **2002**, *149*, S21. (c) Sperry, J. B.; Wright, D. L. *Chem. Soc. Rev.* **2006**, *35*, 605. (d) Yoshida, J.; Kataoka, K.; Horcajada, R.; Nagaki, A. *Chem. Rev.* **2008**, *108*, 2265.

(6) Recent examples: (a) Hayashi, K.; Kim, S.; Chiba, K. *Electrochemistry* **2006**, *74*, 621. (b) Wu, X.; Dube, M. A.; Fry, A. J. *Tetrahedron Lett.* **2006**, *47*, 7667. (c) Tajima, T.; Kurihara, H.; Fuchigami, T. *J. Am. Chem. Soc.* **2007**, *129*, 6680. (d) Mitsudo, K.; Kaide, T.; Nakamoto, E.; Yoshida, K.; Tanaka, H. *J. Am. Chem. Soc.* **2007**, *129*, 2246. (f) Horii, D.; Fuchigami, T.; Atobe, M. *J. Am. Chem. Soc.* **2007**, *129*, 11692. (e) Park, Y. S.; Little, R. D. *Electrochim. Acta* **2009**, *54*, 5077. (f) Kakiuchi, F.; Kochi, T.; Mutsutani, H.; Kobayashi, N.; Urano, S.; Sato, M.; Nishiyama, S.; Tanabe, T. *J. Am. Chem. Soc.* **2009**, *131*, 11310. (g)

Kirste, A.; Schnakenburg, G.; Stecker, F.; Fischer, A.; Waldvogel, S. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 971.

(7) (a) Raoult, E.; Sarrazin, J.; Tallec, A. *J. Appl. Electrochem.* **1984**, *14*, 639. (b) Ogibin, Y. N.; Ilovaiskii, A. I.; Nikisin, G. I. *Russ. Chem. Bull.* **1994**, *43*, 1536. (c) Purgato, F. L. S.; Ferreira, M. I. C.; Romero, J. R. *J. Mol. Catal. A: Chem.* **2000**, *161*, 99. (d) Halas, S. M.; Okyne, K.; Fry, A. J. *Electrochim. Acta* **2003**, *48*, 1837.

(8) (a) Ashikari, Y.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2011**, *133*, 11840. (b) Ashikari, Y.; Nokami, T.; Yoshida, J. *Org. Biomol. Chem.* **2013**, *11*, 3322.

(9) Selected examples of *N*-acyliminium ion pools: (a) Yoshida, J.; Suga, S.; Suzuki, S.; Kinomura, N.; Yamamoto, A.; Fujiwara, K. *J. Am. Chem. Soc.* **1999**, *121*, 9546. (b) Suga, S.; Okajima, M.; Fujiwara, K.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 7941. (c) Suga, S.; Watanabe, M.; Yoshida, J. *J. Am. Chem. Soc.* **2002**, *124*, 14824. (d) Yoshida, J.; Suga, S. *Chem.–Eur. J.* **2002**, *8*, 2651. (e) Maruyama, T.; Mizuno, Y.; Shimizu, I.; Suga, S.; Yoshida, J. *J. Am. Chem. Soc.* **2007**, *129*, 1902. (f) Suga, S.; Shimizu, I.; Ashikari, Y.; Mizuno, Y.; Maruyama, T.; Yoshida, J. *Chem. Lett.* **2008**, *37*, 1008.

(10) Selected examples of alkoxycarbenium ion pools: (a) Suga, S.; Suzuki, S.; Yamamoto, A.; Yoshida, J. *J. Am. Chem. Soc.* **2000**, *122*, 10244. (b) Okajima, M.; Suga, S.; Itami, K.; Yoshida, J. *J. Am. Chem. Soc.* **2005**, *127*, 6930. (c) Suga, S.; Matsumoto, K.; Ueoka, K.; Yoshida, J. *J. Am. Chem. Soc.* **2006**, *128*, 7710.

(11) Selected examples of diarylcarbenium ion pools: (a) Okajima, M.; Soga, K.; Nokami, T.; Suga, S.; Yoshida, J. *Org. Lett.* **2006**, *8*, 5005. (b) Nokami, T.; Ohata, K.; Inoue, M.; Tsuyama, H.; Shibuya, A.; Soga, K.; Okajima, M.; Suga, S.; Yoshida, J. *J. Am. Chem. Soc.* **2008**, *130*, 10864. (c) Okajima, M.; Soga, K.; Watanabe, T.; Terao, K.; Nokami, T.; Suga, S.; Yoshida, J. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 594. (d) Nokami, T.; Watanabe, T.; Musya, N.; Suehiro, T.; Morofuji, T.; Yoshida, J. *Tetrahedron* **2011**, *67*, 4664. (f) Nokami, T.; Watanabe, T.; Musya, N.; Morofuji, T.; Tahara, K.; Tobe, Y.; Yoshida, J. *Chem. Commun.* **2011**, *47*, 5575.

(12) For recent advances within this area: (a) Wang, S.; Lie, F.; Lim, E.; Li, K.; Li, Z. *Adv. Synth. Catal.* **2009**, *351*, 1849. (b) Monfared, H. H.; Kheirabadi, S.; Lalami, N. A.; Mayer, P. *Polyhedron* **2011**, *30*, 1375.

(13) Anodic acetoxylation usually gives monoacetolylation products; see: (a) Srivastav, M. K.; Saraswat, A.; Singh, R. K. P. *Orient. J. Chem.* **2010**, *26*, 61. (b) Tajima, T.; Kishi, Y.; Nakajima, A. *Electrochim. Acta* **2009**, *54*, 5959.

(14) The oxidation potentials were measured by RDE in $LiClO_4/CH_3CN$ using an SCE as a reference electrode.

(15) In the presence of DMSO, a substrate having a higher oxidation potential than that of DMSO is not electrolyzed. See ref 11 and Chapter 1 and 2.

(16) For recent advances within the area: (a) Plietker, B.; Niggemann, A.; Pollrich, A. *Org. Biomol. Chem.* **2004**, *2*, 1116. (b) Emmanuvel, L.; Shaikh, T. M. A.; Sudalai, A. *Org. Lett.* **2005**, *7*, 5071. (c) Plietker, B.; Niggemann, A. *J. Org. Chem.* **2005**, *70*, 2402. (d) de Boer, J. W.; Brinksma, J.; Browne, W. R.; Meetsma, A.; Alsters, P. L.; Hage, R.; Feringa, B. L. *J. Am. Chem. Soc.* **2005**, *127*, 7990. (e) Oldenburg, P. D.; Que, L., Jr. *Catal. Today* **2006**, *117*, 15. (f) Li, Y.; Song, D.; Dong, V. M. *J. Am. Chem. Soc.* **2008**, *130*, 2962. (g) Plietker, B.; Neisius, N. M. *J. Org. Chem.* **2008**, *73*, 3218. (h) de Boer, J. W.; Brinksma, J.; Browne, W. R.; Harutyunyan, S. R.; Bini, L.; Tiemersma-Weyman, T. D.; Alsters, P. L.; Hage, R.; Feringa, B. L. *Chem. Commun.* **2008**, 3747. (i) Wang, A.; Jiang, H.; Chen, H. *J. Am. Chem. Soc.* **2009**, *131*, 3846. (j) Wang, W.; Wang, F.; Shi, M. *Organometallics* **2010**, *29*, 928. (k) Seayad, J.; Seayad, A. M.; Chai, C. L. L. *Org. Lett.* **2010**, *12*, 1412.

(17) Dihydroxylation of alkenes by an electrochemically regenerated Os catalyst was reported: Torii, S.; Liu, P.; Tanaka, H. *Chem. Lett.* **1995**, *24*, 319.

(18) (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (b) Dobler, C.; Mehltretter, G. M.; Sundermeier, U.; Beller, M. *J. Organomet. Chem.* **2001**, *621*, 70.

(19) (a) Adam, W., Ed. *Peroxide Chemistry: Mechanistic and Preparative Aspects of Oxygen Transfer*; Wiley-VCH: Weinheim, Germany, 2000. (b) Rappoport, Z., Ed. *The Chemistry of Peroxides*; Wiley: Chichester, U.K., 2006; Vol. 2.

(20) ^{1}H NMR analysis indicated that the cyclized alkoxysulfonium ion was generated as a single stereoisomer. See ref 11 and Chapter 2.

(21) It was reported that an optically pure alcohol was obtained by hydrolysis of an optically pure alkoxysulfonium ion. See: Ray, D. G., III; Koser, G. F. *J. Am. Chem. Soc.* **1990**, *112*, 5672.

(22) Some recent examples of oxidative alkene cyclization reactions: (a) Jensen, K. H.; Pathak, T. P.; Zhang, Y.; Sigman, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 17074. (b) Pathak, T. P.; Gligorich, K. M.; Welm, B. E.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 7870. (c) McDonald, R. I.; White, P. B.; Weinstein, A. B.; Tam, C. P.; Stahl, S. S. *Org. Lett.* **2011**, *13*, 2830.

(23) For electron-transfer-mediated cyclization reactions: (a) Tokuda, M.; Fujita, H.; Miyamoto, T.; Suginome, H. *Tetrahedron* **1993**, *49*, 2413. (b) Xu, H.-C.; Moeller, K. D. *J. Am. Chem. Soc.* **2008**, *130*, 13542. (c) Liu, L.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2010**, *49*, 3069. (d) Xu, H.-C.; Moeller, K. D. *Angew. Chem., Int. Ed.* **2010**, *49*, 8004. (d) Redden, A.; Moeller, K. D. *Org. Lett.* **2011**, *13*, 1678.

(24) Fenselau, A. M.; Moffatt, J. G. *J. Am. Chem. Soc.* **1966**, *88*, 1762.

(25) Some recent examples of reactions involving a cation intermediate stabilized by an intramolecular nitrogen atom interaction: (a) Ori, M.; Toda, N.; Takami, K.; Tago, K.;

Kogen, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 2540. (b) Krow, G. R.; Gandla, D.; Guo, W.; Centafont, R. A.; Lin, G.; DeBrosse, C.; Sonnet, P. E.; Ross, C. W., III; Ramjit, H. G.; Carroll, P. J.; Cannon, K. C. *J. Org. Chem.* **2008**, *73*, 2114.

(26) The oxidation potentials of the substrates (R= CH_3: 1.34 V vs SCE, R = H: 1.31 V) are less positive than that of 1-phenylpropene (1.42 V). See ref 11 and Chapter 2.

(27) Lovick, H. M.; Michael, F. E. *J. Am. Chem. Soc.* **2010**, *132*, 1249.

(28) Dieskau, A. P.; Begouin, J.-M.; Plietker, B. *Eur. J. Org. Chem.* **2011**, 5291.

(29) Park, Y. H.; Ahn, H. R.; Canturk, B.; Jeon, S., II; Lee, S.; Kang, H.; Molander, G. A.; Ham, J. *Org. Lett.* **2008**, *10*, 1215.

(30) García, D.; Foubelo, F.; Yus, M. *Tetrahedron* **2008**, *64*, 4275.

(31) Wang, K.; Wang, S.-X.; Gao, M.-Z.; Li, J.-T. *Synth. Commun.* **2006**, *36*, 1391.

(32) Zhao, L.; Han, B.; Huang, Z.; Miller, M.; Huang, H.; Malashock, D. S.; Milan, A.; Robertson, D. E.; Weiner, D. P.; Burk, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 11156.

(33) Li, J.-T.; Lin, Z.-P.; Li, T.-S. *Ultrason. Sonochem.* **2005**, *12*, 349.

(34) Green, I. R.; October, N. *Arkivoc* **2010**, 71.

(35) Carteau, D.; Brunerie, P.; Guillemat, B.; Bassani, D. M. *Photochem. Photobial. Sci.* **2007**, *6*, 423.

(36) Lee, J.; Hoang, T.; Lewis, S.; Weissman, S. A.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **2002**, *42*, 6223.

(37) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 6328.

(38) SHELX 97: G. M. Sheldrick, **1997**.

(39) Yadokari-XG: Kabuto, C.; Akine, S.; Nemoto, T.; Kwon, E. *J. Cryst. Soc. Jpn.* **2009**, *51*, 218.

(40) Kokotos, C. G.; Aggarwal, V. K. *Chem. Commun.* **2006**, 2156.

Chapter 4

Halogen and Chalcogen Cation Pools Stabilized by DMSO. Versatile Reagents for Olefin Functionalization

Abstract

Halogen and chalcogen cations (X^+ = Br^+, I^+, ArS^+, and $ArSe^+$) were generated by low temperature electrochemical oxidation in the presence of dimethylsulfoxide (DMSO) and were accumulated in the solution as "cation pools." DFT calculations indicated the higher stabilizing ability of DMSO. The complexes of I^+ with one and two DMSO molecules were observed by cold-spray-ionization MS analyses. The stability of the cation pools increased in the order of Br^+ < I^+ < ArS^+ < $ArSe^+$, which could be explained in terms of the electronegativity of the halogen and chalcogen atoms. The resulting cation pools served as versatile reagents for synthesis. The reactions with alkenes gave β-X-substituted alkoxysulfonium ions, which were converted to the corresponding carbonyl compounds by treatment with triethylamine, whereas the treatment with methanol gave the corresponding alcohols. The reactions with alkenes bearing a tosylamide moiety and 1,6-dienes gave the cyclized products.

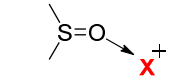
Introduction

Organic molecules bearing halogens and chalcogens not only serve as powerful intermediates in organic syntheses but also functional materials and biologically active compounds.[1] Although a wide variety of methods for introducing such elements into organic molecules have been developed so far, one of the most straightforward and powerful methods would be the use of highly reactive halogen cations and monovalent chalcogen cations.[2] However, such species are usually too unstable to accumulate in the solution, and therefore they are difficult to use as reagents.

The electrochemical oxidation[3,4] provides a powerful method for generating and accumulating highly reactive cationic species in the solution (the "cation pool" method),[3c,5] whereas the chemical methods are not effective because of reversibility of cation generation.[6,7] Although some carbocations and onium ions[8] can be accumulated as cation pools at low temperatures, halogen and chalcogen cations are difficult to accumulate in the solution as "cation pools" because they are too unstable.

One potential method to solve this problem would be the use of a stabilizing agent that coordinates to the cation being generated. The crucial point for the success of this approach is choosing an appropriate stabilizing agent. To date, only a few stabilizing agents have been reported. For example, Miller and co-workers reported the generation and accumulation of "I^+" cation in acetonitrile,[9,10] and later Yoshida and co-workers detected $CH_3CN{-}I^+$ and $(CH_3CN)_2{-}I^+$ by cold-spray-ionization mass spectroscopy.[11] Shono and co-workers reported that "I^+" could be accumulated in trimethyl orthoformate (TMOF), and its reactivity was different from one generated in CH_3CN.[12] Moreover, Yoshida and coworkers reported that arylsulfenium ions (ArS^+) could be accumulated in the presence of diaryl disulfide (ArSSAr).[13] However, more versatile stabilizing agents for a wide variety of reactive cations are needed. This chapter describes that dimethyl sulfoxide (DMSO) can be generally used as a stabilizing agent for halogen and chalcogen cations (Scheme 1) and that the pools of the stabilized cations serve as powerful reagents for alkene difunctionalization. Also, the use of DMSO leads to a useful synthetic transformation, because the alkoxysulfonium ion intermediates can be converted to carbonyl compounds *via* Swern−Moffatt type oxidation[14] described in Chapter 1 and 2,[15] by taking advantage of reaction integration using reactive intermediates.[16,17]

Scheme 1. Halogen and Chalcogen Cations Stabilized by DMSO.



X = Br, I, ArS, and ArSe

Results and Discussions

First, the nature of I^+/DMSO[18] was studied using the computational method (Figure 1).[19,20] For comparison, I^+/CH_3CN and I^+/TMOF systems were also studied. The DFT calculations indicated that I^+ forms a complex with DMSO in the gas phase. The oxygen atom of DMSO interacts with I^+ (I−O distance: 2.09 Å), and the stabilization energy is 118.9 kcal/mol. The coordination by the second DMSO also causes further stabilization (36.1 kcal/mol). The interaction with the third DMSO somewhat stabilizes I^+ (7.5 kcal/mol), but the I−O distance is much longer (3.98 Å),[21] indicating the third DMSO does not directly coordinate to I^+. In the case of CH_3CN, the calculations indicated that I^+ forms a complex with CH_3CN in gas phase, but stabilization energy (101.5 kcal/mol) is smaller than that for DMSO. The further stabilization energy by the second CH_3CN (31.6 kcal/mol) is also smaller than that for DMSO. It is interesting that I^+ does not form a stable complex with a single TMOF molecule in gas phase whereas it forms a stable complex with two molecules of TMOF. However, total stabilization energy with two TMOF (130 kcal/mol) is smaller than those for two DMSO (155 kcal/mol) and two CH_3CN (133 kcal/mol). Therefore, the computational studies indicated that stabilizing ability of DMSO to I^+ is stronger than those of CH_3CN and TMOF.

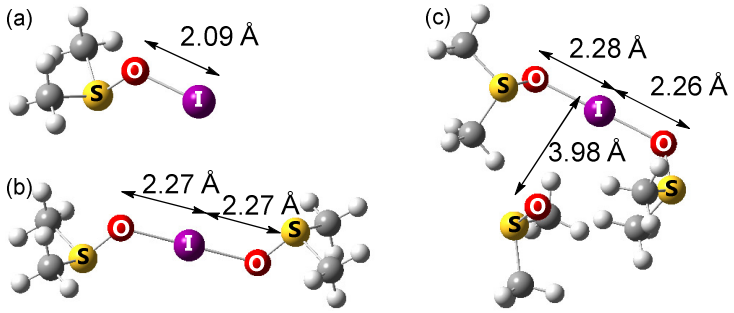


Figure 1. Structures of (a) DMSO–I^+, (b) $(DMSO)_2$–I^+, and (c) $(DMSO)_3$–I^+ indicated by DFT calculation on the level of B3LYP/6-31G(d) and LANL2DZ (with ECP) for I.

With the information obtained by the computational studies in hand, the experimental studies on the generation of I^+/DMSO **(1-I)** cation pool were performed. The electrochemical oxidation of Bu_4NI was carried out in a divided cell in DMSO/CH_2Cl_2 (1:9 v/v) using Bu_4NBF_4 as a supporting electrolyte at –78 °C. After 2.1 F/mol of electricity was consumed, the resulting solution was analyzed by the cold-spray-ionization mass spectroscopy (CSI-MS)[22] at 0 °C, which showed the peaks due to DMSO−I^+ and $(DMSO)_2$−I^+ species (Figure 2, top). (*Z*)-5-Decene (**2a**) was added to the solution and the mixture was stirred at 0 °C. Although **1-I** could not be characterized by NMR, the resulting β-iodo alkoxysulfonium ion **3a-I** could be well

characterized by NMR (Figure 2, bottom). The cross peak of the HMQC spectrum indicated that a signal at 4.18 ppm (^{1}H NMR) is due to the proton (H^a) attached to the carbon (δ = 91.4 ppm in ^{13}C NMR) adjacent to the oxygen atom derived from DMSO. A signal at 4.14 ppm could be assigned to the proton (H^b) attached to the carbon adjacent to the iodine atom. The HMQC spectrum also indicated that two singlet signals at 3.26 and 3.30 ppm (^{1}H NMR) are due to the protons attached to the methyl carbons derived from DMSO. The formation of **3a-I** indicated that **1-I** having the interelement bond[23] served as both a nucleophile and an electrophile toward the carbon−carbon double bond. Treatment of **3a-I** with triethylamine gave α-iodo ketone **4a-I**. It is also noteworthy that the electrochemical oxidation of Bu_4NI in the absence of DMSO at –78 °C followed by the addition of **2a** and DMSO and subsequent treatment with triethylamine did not give **4a-I**, indicating that I^+ could not be accumulated in the solution in the absence of DMSO.

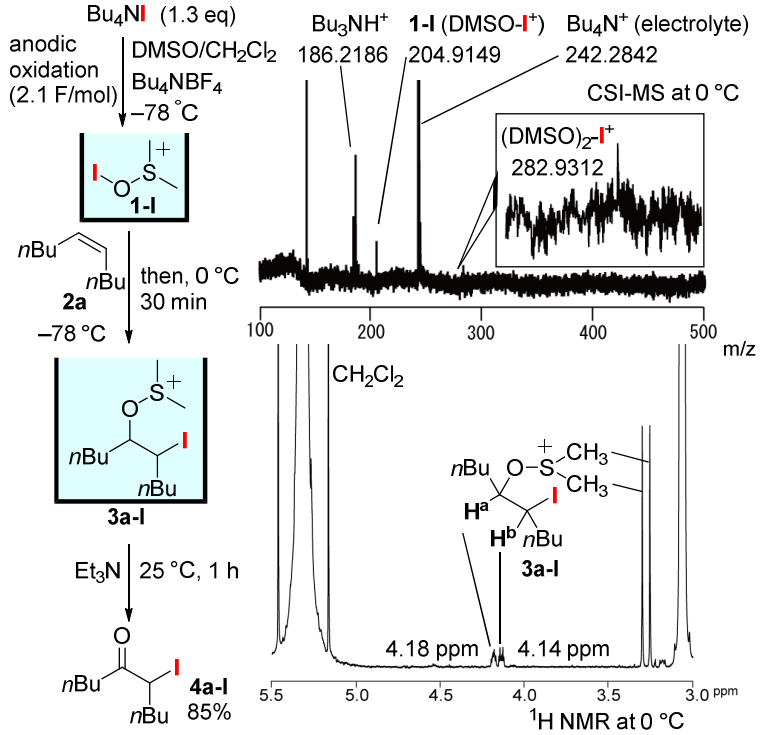


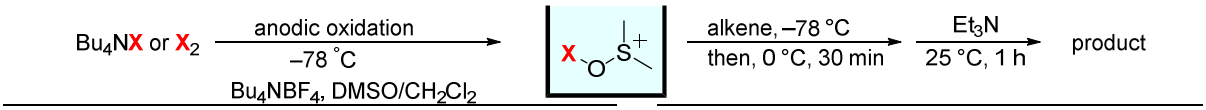
Figure 2. Generation of I^+/DMSO **1-I**, and its reaction with an alkene. CSI-MS and ^{1}H NMR analyses

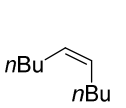
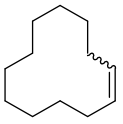
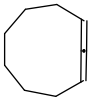
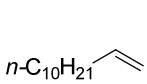
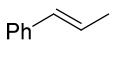
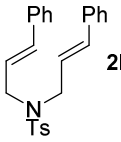
As shown in Table 1, **1-I** reacted with various alkenes to give the corresponding α-iodo ketones. It is noteworthy that the electrochemical oxidation of I_2 instead of Bu_4NI was also effective for generating **1-I** (entry 8).

It is noteworthy that electrochemically generated I^+/CH_3CN and I^+/TMOF are not effective for the present transformation. The reaction of I^+/CH_3CN with **2b** in DMSO/CH_2Cl_2 followed by the treatment with triethylamine gave **4b-I** only in a low yield (39%). The use of I^+/TMOF did not

give **4b-I** at all. The reaction of **2b** with *N*-iodosuccinimide (NIS) in DMSO/CH_2Cl_2 followed by the treatment with triethylamine resulted in recovery of **2b**. I_2, NIS, and NBS with IBX are well-known systems for transforming alkenes to α-halocarbonyl compounds.[24] However, in addition to the advantage of providing mild, easily scalable reaction conditions, the present electrochemical approach seems to be particularly more attractive from safety and environmental standpoints, because the use of hazardous and explosive[25] IBX can be avoided.

Table 1. Reactions of Alkenes with Halogen and Chalcogen Cation Pools Stabilized by DMSO (X^+/DMSO). [a]



entry	alkene	product (yield)[b]		entry	alkene	product (yield)[b]	
1		**4a-Br**	90%	19		**4e-S**	67%
2		**4a-I**	85%	20		**4e-Se**	24%
3		**4a-S**	75%				
4		**4a-Se**	60%				
5		**4b-Br**	quant	21		**4f-S**	37%
6			91%[c]	22		**4f-Se**	80%
7		**4b-I**	95%				
8			84%[d]				
9		**4b-S**	88%				
10		**4b-Se**	91%				
11		**4c-Br**	66%	23		**4g-Br**	88%
12		**4c-I**	75%	24		**4g-I**	89%
13		**4c-S**	80%	25		**4g-S**	41%
14		**4c-Se**	80%	26		**4g-Se**	99%
15		**4d-Br**	77%	27		**4h-Br**	78%
16		**4d-I**	56%	28		**4h-I**	40%
17		**4d-S**	49%	29		**4h-S**	63%
18		**4d-Se**	n.d.	30		**4h-Se**	81%

		4c'-Br	20%
		4c'-I	10%
		4c'-S	14%
		4c'-Se	n.d.
		4d'-Br	n.d.
		4d'-I	14%
		4d'-S	28%
		4d'-Se	63%

[a]The electrolysis of Bu_4NI and Bu_4NBr was carried out using 1.3 equiv of Bu_4NX (based on the alkene which was added after electrolysis) with 2.1 F/mol of electricity based on Bu_4NX. The electrolysis of ArSSAr and ArSeSeAr was carried out using 0.65 equiv of XX_2 (based on the alkene which was added after electrolysis) with 2.1 F/mol of electricity based on X_2. [b]Isolated yield. [c]The electrolysis was carried out using 0.65 equiv of Br_2 (based on the alkene which was added after electrolysis) with 2.1 F/mol of electricity based on Br_2. [d]The electrolysis was carried out using 0.65 equiv of I_2 (based on the amount of the alkene which was added after electrolysis) with 2.1 F/mol of electricity based on I_2.

Next the generation and reactions of Br^+/DMSO (**1-Br**) were examined. DFT calculations indicated that Br^+ is also stabilized by coordination of one or two DMSO molecules like **1-I**. The electrochemical oxidation of Bu_4NBr was carried out in the presence of DMSO at –78 °C. Although **1-Br** was not detected by NMR and CSI-MS analyses, the resulting solution reacted

with **2a** to give α-bromo alkoxysulfonium ion **3a-Br**, which was characterized by ^{1}H and ^{13}C NMR. The subsequent treatment with triethylamine gave α-bromo ketone **4a-Br** (Table 1, entry 1). As shown in Table 1, **1-Br** also reacted with various alkenes to give the corresponding α-bromo ketones. Because α-bromo ketones can be utilized for further transformations such as Favorskii rearrangement[26] and Reformatsky reaction,[27] the present transformation seems to be useful in organic synthesis. Br_2 is also effective as a precursor of **1-Br** (entry 6).

The generation and accumulation of arylchalcogenium ions stabilized by DMSO were then investigated. DFT calculations indicated that the ArS and ArSe are also stabilized by coordination of one or two DMSO molecules. The electrochemical oxidation of di(4-fluorophenyl) disulfide (ArSSAr, Ar = 4-FC_6H_4)[28] and that of diphenyl diselenide (ArSeSeAr, Ar = Ph)[29] at –78 °C followed by the addition of **2a** and subsequent treatment with triethylamine gave α-thio ketone **4a-S** (75%) and α-seleno ketone **4a-Se** (60%), respectively. The results indicated that ArS^+/DMSO[30] and $ArSe^+$/DMSO could be generated and accumulated in the solution as cation pools. It is noteworthy that α-seleno carbonyl compounds such as **4a-Se** are key intermediates of Grieco−Nishizawa elimination reaction[31] and are useful intermediates for the synthesis of α,β-unsaturated carbonyl compounds.

The relative stability of these cationic species was estimated. Thus, the electrochemical oxidation reactions of Bu_4NBr, Bu_4NI, PhSSPh, and PhSeSePh were carried out at –78 °C, and the resulting solutions were warmed to a second temperature. After being kept there for 30 min, the solutions were cooled at –78 °C and were reacted with **2b**. After treatment with triethylamine the yields of the corresponding ketones were determined. Relative stabilities were evaluated by the relative yields based on those not kept at the second temperature. As shown in Figure 3, Br^+ is the least stable. The stability increases in the order of $Br^+ < I^+ < PhS^+ < PhSe^+$. This tendency can be explained in terms of electronegativity of the cationic elements (Br: 2.96, I: 2.66, S: 2.58, and Se: 2.55).[32,33]

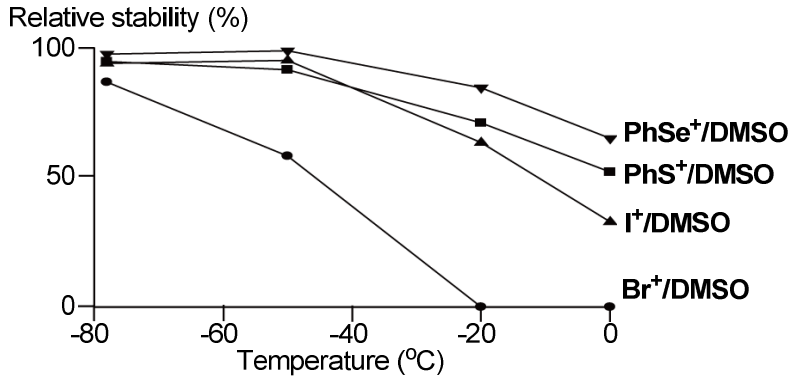
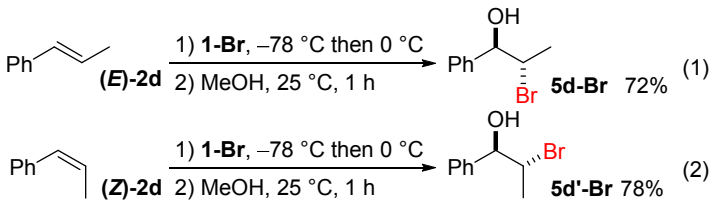


Figure 3. Thermal stability of DMSO–X^+ species.

It is also interesting that the nature of the cationic elements also affected the regioselectivity of the addition to unsymmetrically substituted alkenes. The reaction of **1-Br** with terminal alkene **2c** gave ketone **4c-Br** as a major product and aldehyde **4c'-Br** as a minor product (entry 11). The amount of aldehyde decreased when **1-I** and **1-Se** were used (entries 12 and 13). The reaction of **1-Se** with **2c** gave ketone **4c-Se** exclusively. Aldehyde **4c'-Se** was not observed (entry 14). Low selectivity of **1-Br** might be explained in terms of higher reactivity of the three-membered ring bromonium ion intermediate than others, leading to less regioselective nucleophilic attack by DMSO.[34]

The regioselectivity for 1-phenyl-1-propene (**2d**) was more interesting. The reaction of **1-Br** with **2d** gave 2-bromo-1-phenylpropan-1-one (**4d-Br**) selectively (entry 15), whereas the reaction of **1-Se** with **2d** gave 1-phenyl-1-(phenylselanyl)propan-2-one (**4d'-Se**) selectively (entry 18). **1-I** and **1-S** gave mixtures of two products (entries 16 and 17). This remarkable contrast in regioselectivity might be explained in terms of the difference in electronegativity of the halogen and chalcogen atom, although the detailed mechanism is not yet clear. The reaction of **1-Br** with **2d** would give the three-membered ring bromonium ion. However, a positive charge seems to be located mainly on the benzylic carbon rather than the electronegative Br. Therefore, DMSO attacks the benzylic carbon to give phenyl ketone **4d-Br** after treatment with triethylamine. The Natural Bond Orbital (NBO) analysis[35] is consistent with this idea.[36] The charge on the halogen and chalcogen atom of the three-membered ring onium ion intermediate decreases in the order of Se > S > I > Br, whereas the charge on the benzylic carbon increases in the order of Se < S < I < Br. The bond order between the halogen and chalcogen atom with the benzylic carbon also decreases in the order of Se > S > I > Br.

Stereochemistry of the addition to carbon−carbon double bonds is another intriguing aspect of the chemistry of X^+/DMSO, although the stereochemistry is destroyed during Swern−Moffatt type oxidation. To gain the information of the stereochemistry, an alkoxysulfonium ion intermediate was treated with methanol instead of triethylamine. Thus, both *E* and *Z* isomers of **2d** were reacted with **1-Br** and the resulting solution was treated with methanol.[37] (*E*)-**2d** gave **5d-Br** (eq 1), whereas (*Z*)-**2d** gave its diastereomer **5d'-Br** (eq 2), suggesting the addition of Br^+ and DMSO across the carbon−carbon double bond in an *anti* fashion, because it is known that methanol attacks the sulfur atom to cleave the oxygen−sulfur bond.[37] The *anti*-selectivity suggests a mechanism involving the back-side attack of DMSO in the bulk solution on the three-membered ring bromonium ion generated from Br^+ and an alkene.

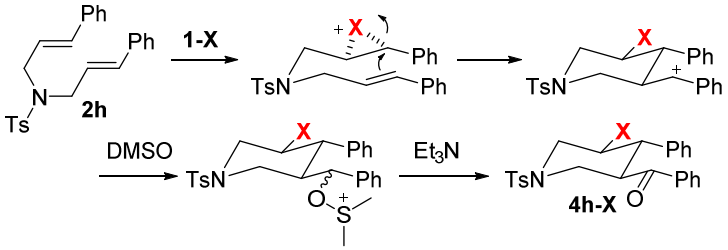


1,3-Dienes reacted with **1-S** and **1-Se** to give α,β-unsaturated carbonyl compounds in moderate yields after treatment with triethylamine (entries 19 and 20), although the reactions with **1-Br** and **1-I** gave complex mixtures. The regiochemistry is stimulating. DMSO attacked the inner carbon of the 1,3-diene selectively to give the 1,2-addition intermediate. The product derived from 1,4-addition was not obtained. Allenes also reacted with **1-S** and **1-Se** to give α,β-unsaturated carbonyl compounds (entries 21 and 22). In this case, DMSO attacked the terminal carbon of the allene selectively.

It is also stimulating that halogen and chalcogen cation pools initiate alkene-cyclization reactions. Reactions of **1-X** with an alkene having a nucleophilic tosylamide group (**2g**) gave the cyclized pyrrolidine derivatives (entries 23–26), which are useful building blocks of biologically interesting compounds.[38] In these cases, DMSO was not incorporated into the product because the intramolecular tosylmaide group acted as a nucleophile.

The reaction of **1-X** with 1,6-diene **2h** is more fascinating. The cyclized products **4h-X**, piperidine derivatives[38] having both the X substituent and a carbonyl group were obtained as a single diastereomer after treatment with triethylamine (entries 27–30). The diastereoselectivity indicates that the three-membered ring onium ion generated by the attack of one of the carbon−carbon double bonds of **2h** on X^+ was subjected by the nucleophilic attack by the other carbon−carbon double bond to give the cyclized cation through a chairlike transition state as shown in Scheme 2.[39] This mechanism is similar to that for polyene cyclization reactions, implying the feasibility of halogen and chalcogen cation pools initiated polycyclization for a synthesis of polycyclic compounds.[3,40]

Scheme 2. Plausible Mechanism of the Reactions of **1-X** with **2h**.



Conclusion

In conclusion, it was found that halogen cations (Br^+ and I^+) and monovalent chalcogen cations (ArS^+ and $ArSe^+$) stabilized by DMSO can be generated and accumulated as cation pools by low temperature electrochemical oxidations. The cations have both sufficient stability and

marked reactivity toward alkenes. The reactions with alkenes gave the corresponding carbonyl compounds bearing a halogen or chalcogen substituent at the α-carbon after treatment with triethylamine. The reactions could be combined with alkene cyclization to serve useful methods for synthesis of cyclic compounds. These findings proved that this new tactic based on halogen and chalcogen cations stabilized by DMSO will provide an access to a wide range of chemical processes for making synthetic intermediates having halogen and chalcogen atoms.

Experimental Section

General Remarks. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Varian MERCURY plus-400 (^{1}H 400 MHz, ^{13}C 100 MHz), or JEOL ECA-600P spectrometer (^{1}H 600 MHz, ^{13}C 150 MHz) Chemical shifts are recorded using tetramethylsilane as an internal standard for ^{1}H NMR (0.0 ppm), and methin signal of $CHCl_3$ for ^{13}C NMR (77.0 ppm) unless otherwise noted. Mass spectra were obtained on JEOL EXACTIVE (ESI and APCI), and JEOL JMS-SX102A mass spectrometer (EI). Cold-spray ionization (CSI) mass spectra were recorded on JEOL JMS-T100CSK spectrometer. Preparative gel permeation chromatography (GPC) was carried out on Japan Analytical Industry LC-918 equipped with JAIGEL-1H and 2H using $CHCl_3$ as an eluent. Merck precoated silica gel F_{254} plates (thickness 0.25 mm) was used for thin-layer chromatography (TLC) analysis. Flash chromatography was carried out on a silica gel (Kanto Chem. Co., Silica Gel N, spherical, neutral, 40–100 mm). All reactions were carried out under argon atmosphere unless otherwise noted. The anodic oxidation was carried out using an H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon GF-20-P21E, ca. 160 mg, dried at 300 ^{o}C/1 mmHg for 3 hours before use) and a platinum plate cathode (10 mm x 10 mm). DFT calculations were performed with the Gaussian 09 program.[41] All geometry optimizations were carried out at the RB3LYP level of density functional theory with the basis set of 6-31G(d) and LANL2DZ (with ECP) for I, and with the basis set of 6-311++G(2df,2pd), and SDB-cc-pVTZ (with ECP) for I.

Materials. Compounds **2f**,[42] **2g**,[43] **2h**,[15(a)] and di(4-fluorophenyl)disulfide[13(a)] were prepared according to the reported procedures. Bu_4NBF_4 was purchased from TCI and dried at 50 ^{o}C/1 mmHg for 12 hours. Dichloromethane was washed with water, distilled from P_2O_5, redistilled from dried K_2CO_3 to remove a trace amount of acid, and stored over molecular sieves 4A. Dimethyl sulfoxide (DMSO) was dried over molecular sieves 4A before use. Triethylamine (Et_3N) was refluxed with calcium hydride, distilled, and stored over molecular sieves 4A. CD_2Cl_2 was dried over molecular sieves 4A before use. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification.

CSI-MS analysis. In the anodic chamber were placed iodine (126.0 mg, 0.496 mmol), Bu_4NBF_4 (330 mg), DMSO (1.0 mL), and CH_2Cl_2 (9.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (120 μL), Bu_4NBF_4 (330 mg), and CH_2Cl_2 (10.0 mL). The constant current electrolysis (35 mA) was carried out at –78 ^{o}C with magnetic stirring until 2.1 F/mol of electricity was consumed. The reaction mixture of the anodic chamber was analyzed by CSI-MS (spray temperature; 0 ^{o}C): HRMS (CSI) m/z calcd for C_2H_6OSI (DMSO–I^+): 204.9179, found 204.9149, m/z calcd for $C_4H_{12}O_2S_2I$ ((DMSO)$_2$–I^+): 282.9318, found 282.9312.

Low temperature NMR analysis of alkoxysulfonium ion 3a-I. In the anodic chamber were placed tetra-*n*-butylammonium iodide (47.5 mg, 0.129 mmol), Bu_4NBF_4 (490 mg), DMSO (0.5 mL), and CH_2Cl_2 (4.5 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (30 μL), Bu_4NBF_4 (490 mg), and CH_2Cl_2 (5.0 mL). The constant current electrolysis (4.0 mA) was carried out at –78 °C with magnetic stirring until 2.1 F/mol of electricity was consumed. To the anodic chamber was added a solution of (*Z*)-5-decene (**2a**) (13.5 mg, 0.096 mmol) in CD_2Cl_2 (0.5 mL), and to the cathodic chamber 0.5 mL of CH_2Cl_2 was added at –78 °C. The solution was stirred for 30 min at –78 °C, and then was stirred for 30 min at 0 °C. The reaction mixture of the anodic chamber (0.6 mL) was transferred to a 5 mm ϕ NMR tube with septum cap under argon atmosphere at 0 °C. Chemical shifts are reported using methylene signals of CH_2Cl_2 at δ 5.32 as an internal standard. Selected signals for **3a-I** at 0 °C: ^{1}H NMR (600 MHz, CD_2Cl_2) δ 3.26 (s, 3 H), 3.30 (s, 3 H), 4.14 (dt, *J* = 3.6, 10.3 Hz, 1 H), 4.18 (dd, *J* = 6.2, 10.0 Hz, 1 H); ^{13}C NMR (150 MHz, CD_2Cl_2) δ 13.3, 13.4, 21.4, 21.9, 26.4, 31.2, 33.2, 35.3, 35.6, 59.2, 91.4.

Low temperature NMR analysis of alkoxysulfonium ion 3a-Br. In the anodic chamber were placed tetra-*n*-butylammonium bromide (83.7 mg, 0.260 mmol), Bu_4NBF_4 (490 mg), DMSO (0.5 mL), and CD_2Cl_2 (4.5 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (60 μL), Bu_4NBF_4 (490 mg), and CD_2Cl_2 (5.0 mL). The constant current electrolysis (4.0 mA) was carried out at –78 °C with magnetic stirring until 2.1 F/mol of electricity was consumed. The reaction mixture of the anodic chamber (0.6 mL) was transferred to a 5 mm ϕ NMR tube with septum cap under argon atmosphere at –78 °C. (*E*)-5-decene (**3a**) (5.6 μL, 0.030 mmol) was added to the NMR tube and stored at –78 °C. Chemical shifts are reported using methylene signals of CH_2Cl_2 at δ 5.32 as an internal standard. Selected signals for **3a-Br** at –80 °C: ^{1}H NMR (600 MHz, CD_2Cl_2) δ 0.79 (t, *J* = 6.8 Hz, 6 H), 3.18 (s, 3 H), 3.24 (s, 3 H), 4.04 (ddd, *J* = 3.2, 6.2, 10.0 Hz, 1 H), 4.51 (dd, *J* = 5.8, 12.4 Hz, 1 H); ^{13}C NMR (150 MHz, CD_2Cl_2) δ 13.6, 13.7, 21.6, 22.2, 26.0, 28.8, 31.8, 35.0, 35.3, 58.0, 90.8.

Typical procedure for the generation of 1-I and 1-Br and for their reactions. In the anodic chamber were placed tetra-*n*-butylammonium iodide (91.3 mg, 0.247 mmol), Bu_4NBF_4 (980 mg, 3.0 mmol), DMSO (1 mL), and CH_2Cl_2 (9 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (60 μL, 0.68 mmol) and 0.3 M Bu_4NBF_4/CH_2Cl_2 (10 mL). The constant current electrolysis (8.0 mA) was carried out at –78 °C with magnetic stirring until 2.1 F/mol of electricity was consumed. To the anodic chamber was added a solution of (*E*)-5-decene (**3a**) (28.3 mg, 0.202 mmol) in CH_2Cl_2 (0.5 mL), and to the cathodic chamber 0.5 mL of CH_2Cl_2 was added at –78 °C. The solution was stirred for 30 min at –78 °C, and then was stirred for 30 min at 0 °C. Then triethylamine (0.1 mL) was added to both the anodic and cathodic chambers, and the resulting mixture was allowed to be warmed to 25 °C and stirred for additional 1 hour.

The solution in the anodic chambers was collected and the solvent was removed under reduced pressure. Then, the residue was filtered through a short column (2 x 4 cm) of silica gel to remove Bu_4NBF_4 by using hexane/EtOAc (1:1) as an eluent. After removal of the solvent under reduced pressure the crude product was purified by flash chromatography (hexane/EtOAc 100:1 to 50:1) to obtain **6-iododecan-5-one** (**4a-I**) in 85% yield (48.4 mg, 0.172 mmol). TLC R_f 0.63 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.2 Hz, 3 H), 0.93 (t, *J* = 7.2 Hz, 3 H), 1.20–1.40 (m, 6 H), 1.62 (m, 2 H), 1.93 (m, 2 H), 2.63 (dt, *J* = 7.2, 16.8 Hz, 1 H), 2.79 (dt, *J* = 7.2, 16.8 Hz, 1 H), 4.45 (t, *J* = 7.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.82, 13.83, 22.0, 22.2, 26.4, 31.5, 32.9, 34.1, 38.6, 205.0; HRMS (ESI) calcd for $C_{10}H_{19}OI$ [M+H$^+$]: 283.0553, found: 283.0547.

2-Iodocyclododecan-1-one (4b-I). Electrochemical oxidation (2.1 F/mol) of tetra-*n*-butylammonium iodide (74.3 mg, 0.201 mmol), subsequent addition of the solution of cyclododecene (**2b**) (*E*/*Z* mixture, 21.3 mg, 0.128 mmol) in CH_2Cl_2 (0.5 mL), and treatment with Et_3N followed by flash chromatography (hexane/EtOAc 20:1) gave the title compound (37.4 mg, 95%); TLC R_f 0.72 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90–0.94 (m, 6 H), 1.31–1.48 (m, 6 H), 1.57 (m, 3 H), 1.91–2.05 (m, 3 H), 2.67 (m, 2 H), 4.24 (dd, *J* = 6.8, 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 13.8, 22.1, 22.2, 26.0, 29.5, 33.2, 38.7, 53.8, 204.5; HRMS (ESI) calcd for $C_{10}H_{20}OBr$ [M+H$^+$]: 235.0692, found: 235.0689.

The case of iodine as a cation precursor: electrochemical oxidation (2.1 F/mol) of iodine (34.9 mg, 0.138 mmol), subsequent addition of the solution of cyclododecene (**2b**) (*E*/*Z* mixture, 33.3 mg, 0.200 mmol) in CH_2Cl_2 (0.5 mL), and treatment with Et_3N followed by flash chromatography (hexane/EtOAc 20:1) gave the title compound (52.0 mg, 84%).

1-Iododecan-2-one (4c-I). Electrochemical oxidation (2.1 F/mol) of tetra-*n*-butylammonium iodide (91.0 mg, 0.246 mmol), subsequent addition of the solution of 1-dodecene (**2c**) (32.8 mg, 0.195 mmol) in CH_2Cl_2 (0.5 mL), and treatment with Et_3N followed by flash chromatography (hexane/EtOAc 100:1 to 50:1) gave the title compound (45.4 mg, 75%); TLC R_f 0.65 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.8 Hz, 3 H), 1.28 (m, 14 H), 1.62 (m, 2 H), 2.71 (t, *J* = 7,2 Hz, 2 H), 3.80 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.2, 14.1, 22.6, 24.2, 29.0, 29.3, 29.4, 29.5, 31.9, 39.3, 203.3; HRMS (APCI) calcd for $C_{12}H_{24}OI$ [M+H$^+$]: 311.0866, 312.0900, found: 311.0860, 312.0892.

2-Iodo-1-phenylpropan-1-one (4d-I). Electrochemical oxidation (2.1 F/mol) of tetra-*n*-butylammonium iodide (91.1 mg, 0.247 mmol), subsequent addition of the solution of *trans*-β-methylstyrene (**2d**) (21.7 mg, 0.184 mmol) in CH_2Cl_2 (0.5 mL), and treatment with Et_3N followed by flash chromatography (hexane/EtOAc 20:1) gave the title compound (27.0 mg,

56%); TLC R_f 0.55 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08 (d, *J* = 6.8 Hz, 3 H), 5.50 (q, *J* = 6.8 Hz, 1 H), 7.48 (m, 2 H), 7.58 (m, 1 H), 8.01 (dd, *J* = 0.8, 9.2 Hz, 2 H). The spectra were in agreement with the literature.[44]

***N*-Tosyl-2-iodomethylpyrrolidine (4g-I).** Electrochemical oxidation (2.1 F/mol) of tetra-*n*-butylammonium iodide (89.8 mg, 0.243 mmol), subsequent addition of the solution of *N*-tosyl-4-penten-1-amine (**2g**) (47.7 mg, 0.199 mmol) in CH_2Cl_2 (0.5 mL), and treatment with Et_3N followed by flash chromatography (hexane/EtOAc 10:1 to 5:1) gave the title compound (64.7 mg, 89%); TLC R_f 0.37 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (m, 1 H), 1.85 (m, 3 H), 2.44 (s, 3 H), 3.17 (m, 1 H), 3.22 (t, *J* = 9.6 Hz, 1 H), 3.50 (m, 1 H), 3.62 (dd, *J* = 2.8, 9.6 Hz, 1 H) 3.75 (m, 1 H), 7.34 (dd, *J* = 0.4, 8.4 Hz, 2 H), 7.73 (dd, *J* = 2.0, 6.8 Hz, 2 H). The spectra were in agreement with the literature.[45]

(3*R,4*S**,5*S**)-*N*-Tosyl-3-benzoyl-5-iodo-4-phenylpiperidine (4h-I).** Electrochemical oxidation (2.1 F/mol) of tetra-*n*-butylammonium iodide (44.4 mg, 0.120 mmol), subsequent addition of the solution of dicinnamyltosylamine (**2h**) (40.3 mg, 0.100 mmol) in CH_2Cl_2 (0.5 mL), and treatment with Et_3N followed by flash chromatography (hexane/EtOAc 10:1 to 5:1) gave the title compound (22.0 mg, 40%); TLC R_f 0.39 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3 H), 2.64 (dd, *J* = 11.2, 12.0 Hz, 1 H), 2.96 (dd, *J* = 11.6, 11.6 Hz, 1 H), 3.27 (dd, *J* = 11.2, 11.2 Hz, 1 H), 4.10 (m, 2 H), 4.42 (m, 2 H), 7.09 (m, 3 H), 7.17 (m, 2 H), 7.34 (m, 4 H), 7.46 (m, 1 H), 7.66 (m, 4 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 29.6, 49.1, 50.6, 54.1, 55.5, 127.5, 127.7, 128.1, 128.58, 128.62, 130.1, 133.2, 133.7, 135.6, 140.5, 144.3, 198.5; HRMS (ESI) calcd for $C_{25}H_{25}INO_3S$ [M+H$^+$]: 546.0594, found: 546.0587. The stereochemistry on the piperidine ring was analogized by that of **4h-Br**, which was determined by NOE analyses.

6-bromodecan-5-one (**4a-Br**). Electrochemical oxidation (2.1 F/mol) of tetra-*n*-butylammonium bromide (82.3 mg, 0.255 mmol), subsequent addition of a solution of (*Z*)-5-decene (**2a**) (27.0 mg, 0.192 mmol) in CH_2Cl_2 (0.5 mL), and treatment with Et_3N followed by flash chromatography (hexane/EtOAc 100:0 to 10:1) gave the title compound (35.8 mg, 90%). TLC R_f 0.79 (hexane/EtOAc 5:1), R_f 0.09 (hexane): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90–0.94 (m, 6 H), 1.31–1.48 (m, 6 H), 1.57 (m, 3 H), 1.91–2.05 (m, 3 H), 2.67 (m, 2 H), 4.24 (dd, *J* = 6.8, 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 13.8, 22.1, 22.2, 26.0, 29.5, 33.2, 38.7, 53.8, 204.5; HRMS (ESI) calcd for $C_{10}H_{20}OBr$ [M+H$^+$]: 235.0692, found: 235.0689.

2-Bromocyclododecan-1-one (4b-Br). Electrochemical oxidation (2.1 F/mol) of tetra-*n*-butylammonium bromide (82.4 mg, 0.256 mmol), subsequent addition of the solution of cyclododecene (**2b**) (*E*/*Z* mixture, 33.4 mg, 0.201 mmol) in CH_2Cl_2 (0.5 mL), and treatment with

Et_3N followed by flash chromatography (hexane/EtOAc 50:1 to 10:1) gave the title compound (53.1 mg, quant); TLC R_f 0.68 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22–1.35 (m, 14 H), 1.58 (m, 1 H), 1.82–2.03 (m, 2 H), 2.30 (m, 1 H), 2.71 (ddd, *J* = 3.6, 11.6, 16.4 Hz, 1 H), 2.81 (ddd, *J* = 3.6, 6.8, 16.4 Hz, 1 H), 4.39 (dd, *J* = 4.0, 11.6 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.1, 22.4, 23.7, 23.7, 24.0, 24.1, 25.1, 25.3, 33.5, 35.2, 51.6, 205.5; HRMS (ESI) calcd for $C_{12}H_{22}OBr$ [M+H$^+$]: 261.0849, 263.0823, found: 261.0838, 263.0828.

The case of bromine as a cation precursor: electrochemical oxidation (2.1 F/mol) of bromine (6.5 μL, 0.112 mmol), subsequent addition of the solution of cyclododecene (**2b**) (*E*/*Z* mixture, 32.8, 0.195 mmol) in CH_2Cl_2 (0.5 mL), and treatment with Et_3N followed by flash chromatography (hexane/EtOAc 100:1 to 20:1) gave the title compound (46.5 mg, 91%).

1-Bromododecan-2-one (4c-Br). Electrochemical oxidation (2.1 F/mol) of tetra-*n*-butylammonium bromide (83.2 mg, 0.258 mmol), subsequent addition of the solution of 1-dodecene (**2c**) (33.3 mg, 0.198 mmol) in CH_2Cl_2 (0.5 mL), and treatment with Et_3N followed by flash chromatography (hexane to hexane/EtOAc 5:1) and GPC gave the title compound (34.6 mg, 66%); TLC R_f 0.68 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.2 Hz, 3 H), 1.26–1.29 (m, 14 H), 1.62 (m, 2 H), 2.65 (t, *J* = 7.2 Hz, 2 H), 3.89 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 23.8, 29.0, 29.26, 29.29, 29.4, 29.5, 31.8, 34.3, 39.8, 202.3; HRMS (ESI) calcd for $C_{12}H_{24}OBr$ [M+H$^+$]: 263.1005, 265.0985, found: 263.1006, 265.0985.

2-Bromododecanal (4c'-Br). Isolated as above (10.5 mg, 20%); TLC R_f 0.68 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.2 Hz, 3 H), 1.26 (m, 14 H), 1.40 (m, 1 H), 1.52 (m, 1 H), 1.92 (m, 1 H), 2.03 (m, 1 H), 4.21 (ddd, *J* = 3.2, 6.4, 9.2 Hz, 1 H), 9.43 (dd, *J* = 0.8, 3.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 26.9, 28.9, 29.3, 29.4, 29.5, 31.6, 31.9, 55.5, 192.9; HRMS (EI) calcd for $C_{12}H_{23}OBr$ [M$^+$]: 262.0932, found: 262.0930.

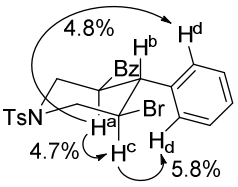
2-Bromo-1-phenylpropan-1-one (4d-Br). Electrochemical oxidation (2.1 F/mol) of tetra-*n*-butylammonium bromide (81.0 mg, 0.251 mmol), subsequent addition of the solution of *trans*-β-methylstyrene (**2d**) (24.1 mg, 0.204 mmol) in CH_2Cl_2 (0.5 mL), and treatment with Et_3N followed by flash chromatography (hexane/EtOAc 15:1) gave the title compound (33.6 mg, 77%); TLC R_f 0.58 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91 (d, *J* = 6.8 Hz, 3 H), 5.30 (q, *J* = 6.4 Hz, 1 H), 7.49 (t, *J* = 7.6 Hz, 2 H), 7.60 (t, *J* = 7.6 Hz, 1 H), 8.03 (dd, *J* = 1.2, 8.4 Hz, 2 H). The spectra were in agreement with the literature.[46]

***N*-Tosyl-2-bromomethylpyrrolidine (4g-Br).** Electrochemical oxidation (2.1 F/mol) of tetra-*n*-butylammonium bromide (83.4 mg, 0.259 mmol), subsequent addition of the solution of *N*-tosyl-4-penten-1-amine (**2g**) (48.1 mg, 0.201 mmol) in CH_2Cl_2 (0.5 mL), and treatment with

Et_3N followed by flash chromatography (hexane/EtOAc 5:1) gave the title compound (56.3 mg, 88%); TLC R_f 0.27 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55 (m, 1 H), 1.73 (m, 1 H), 1.84 (m, 1 H), 1.93 (m, 1 H), 2.44 (s, 3 H), 3.15 (dt, *J* = 10.0, 7.2 Hz, 1 H), 3.36 (t, *J* = 9.6 Hz, 1 H), 3.48 (ddd, *J* = 5.2, 7.2, 14.4 Hz, 1 H), 3.77 (d, *J* = 3.2, 10.4 Hz, 1 H), 3.82 (m, 1 H), 7.34 (dd, *J* = 0.4, 8.4 Hz, 2 H), 7.73 (dd, *J* = 1.6, 6.4 Hz, 2 H). The spectra were in agreement with the literature.[2c]

(3*R,4*S**,5*S**)-*N*-Tosyl-3-benzoyl-5-bromo-4-phenylpiperidine (4h-Br).** Electrochemical oxidation (2.1 F/mol) of tetra-*n*-butylammonium bromide (81.6 mg, 0.253 mmol), subsequent addition of the solution of dicinnamyltosylamine (**2h**) (81.7 mg, 0.202 mmol) in CH_2Cl_2 (0.5 mL), and treatment with Et_3N followed by wash with hexane/EtOAc/$CHCl_3$ gave the title compound (78.5 mg, 78%); TLC R_f 0.26 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3 H), 2.59 (dd, *J* = 11.6, 11.6 Hz, 1 H), 2.79 (ddd, *J* = 2.0, 11.6, 12.0 Hz, 1 H), 3.23 (dd, *J* = 11.2, 11.2 Hz, 1 H), 4.04 (m, 1 H), 4.14 (ddd, *J* = 4.4, 10.8, 10.8 Hz, 1 H), 4.40 (m, 2 H), 7.14 (m, 5 H), 7.34 (m, 4 H), 7.48 (t, *J* = 7.6 Hz, 1 H), 7.66 (d, *J* = 8.4 Hz, 2 H), 7.67 (d, *J* 8.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 49.1, 50.0, 50.4, 53.1, 53.6, 127.56, 127.63, 127.9, 128.2, 128.6, 128.7, 130.1, 133.1, 133.7, 135.8, 139.0, 144.4, 198.3; HRMS (ESI) calcd for $C_{25}H_{25}BrNO_3S$ [M+H$^+$]: 498.0733, found: 498.0705. The stereochemistry was determined by NOE analysis.

NOE analysis of 4h-Br. The NOE analyses indicated the steric interaction between H^a (at 3-position of the piperidine ring) with H^c and H^d. It suggests the protons at 3-, 4-, and 5-position of piperidine ring of **4h-Br** (H^a, H^b, and H^c) are on axial positions, indicating *trans*,*trans*-configration.



Typical procedure for hydroxylation of alkoxysulfonium ions generated from 1-Br. In the anodic chamber were placed tetra-*n*-butylammonium bromide (83.4 mg, 0.259 mmol), Bu_4NBF_4 (980 mg, 3.0 mmol), DMSO (1 mL), and CH_2Cl_2 (9 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (60 μL, 0.68 mmol) and 0.3 M Bu_4NBF_4/CH_2Cl_2 (10 mL). The constant current electrolysis (8.0 mA) was carried out at –78 ^{o}C with magnetic stirring until 2.1 F/mol of electricity was consumed. To the anodic chamber was added a solution of *trans*-β-methylstyrene (**(*E*)-2d**) (23.1 mg, 0.195 mmol) in CH_2Cl_2 (0.5 mL), and to the cathodic chamber 0.5 mL of CH_2Cl_2 was added at –78 ^{o}C. The solution was stirred for 30 min at –78 ^{o}C, and then was stirred for 30 min at 0 ^{o}C. Then methanol (0.5 mL) was added to both the anodic and cathodic chambers, and the resulting mixture was allowed to be warmed to 25 ^{o}C and stirred for additional 1 hour. The solution in the anodic chambers was collected and the solvent was removed under reduced pressure. Then, the residue was filtered through a short column (2 x 4 cm) of silica gel to remove Bu_4NBF_4 by using hexane/EtOAc (1:1) as an eluent. After removal of

the solvent under reduced pressure the crude product was purified by flash chromatography (hexane/EtOAc 5:1) to obtain **(1*S**,2*S**)-2-bromo-1-phenyl-1-propanol** (**5d-Br**) in 72% yield (30.4 mg, 0.141 mmol). TLC R_f 0.36 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55 (d, *J* = 6.8 Hz, 3 H), 2.50 (d, *J* = 3.2 Hz, 1 H), 4.43 (dq, *J* = 3.6, 6.8 Hz, 1 H), 5.02 (m, 1 H), 7.31 (m, 1 H), 7.37 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 56.1, 77.3, 126.3, 128.0, 128.4, 139.5. The spectra were in agreement with the literature.[47]

(1*S,2*R**)-2-Bromo-1-phenyl-1-propanol (5d'-Br).** Electrochemical oxidation (2.1 F/mol) of tetra-*n*-butylammonium bromide (82.3 mg, 0.255 mmol), subsequent addition of the solution of *cis*-β-methylstyrene (**(*Z*)-2d**) (21.3 mg, 0.180 mmol) in CH_2Cl_2 (0.5 mL), and treatment with methanol followed by flash chromatography (hexane/EtOAc 10:1 to 5:1) gave the title compound (30.2 mg, 78%); TLC R_f 0.38 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (d, *J* = 6.8 Hz, 3 H), 2.80 (d, *J* = 3.6 Hz, 1 H), 4.33 (quint, *J* = 6.8 Hz, 1 H), 4.60 (dd, *J* = 3.6, 6.8 Hz, 1 H), 7.35 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 58.4, 79.1, 126.7, 128.45, 128.56, 139.6; HRMS (EI) calcd for $C_9H_{12}OBr$ [M^+]: 213.9993, found: 214.0001.

Typical procedure for the generation of 1-S and 1-Se, and their reactions. In the anodic chamber were placed di(4-fluorophenyl)disulfide (31.4 mg, 0.123 mmol), Bu_4NBF_4 (980 mg, 3.0 mmol), DMSO (1 mL), and CH_2Cl_2 (9 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (30 μL, 0.34 mmol) and 0.3 M Bu_4NBF_4/CH_2Cl_2 (10 mL). The constant current electrolysis (8.0 mA) was carried out at –78 °C with magnetic stirring until 2.1 F/mol of electricity was consumed. To the anodic chamber was added a solution of (*Z*)-5-decene (**2a**) (31.4 mg, 0.202 mmol) in CH_2Cl_2 (0.5 mL), and to the cathodic chamber 0.5 mL of CH_2Cl_2 was added at –78 °C. The solution was stirred for 30 min at –78 °C, and then was stirred for 30 min at 0 °C. Then triethylamine (0.1 mL) was added to both the anodic and cathodic chambers, and the resulting mixture was allowed to be warmed to 25 °C and stirred for additional 1 hour. The solution in the anodic chambers was collected and the solvent was removed under reduced pressure. Then, the residue was filtered through a short column (2 x 4 cm) of silica gel to remove Bu_4NBF_4 by using hexane/EtOAc (1:1) as an eluent. After removal of the solvent under reduced pressure the crude product was purified by flash chromatography (hexane/EtOAc 20:1) to obtain **6-(4-fluorophenylthio)decan-5-one** (**4a-S**) in 75% yield (42.9 mg, 0.152 mmol). TLC R_f 0.63 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.2 Hz, 3 H), 0.90 (t, *J* = 7.2 Hz, 3 H), 1.28–1.35 (m, 5 H), 1.42 (m, 1 H), 1.54 (m, 2 H), 1.62 (m, 1 H), 1.75 (m, 1 H), 2.57 (dt, *J* = 2.4, 7.6 Hz, 2 H), 3.52 (t, *J* = 7.6 Hz, 1 H), 6.99 (t, *J* = 8.8 Hz, 2 H), 7.34 (dd, *J* = 5.2, 8.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 13.8 22.3, 22.4, 26.0, 29.4, 29.8, 39.3, 57.2, 116.1 (d, *J* = 21.8 Hz), 127.6 (d, *J* = 3.5 Hz), 135.7 (d, *J* = 8.3 Hz), 162.8 (d, *J* = 254.5 Hz), 207.1; HRMS (ESI) calcd for $C_{16}H_{24}OFS$ [$M+H^+$]: 283.1526, found: 283.1520.

2-(4-Fluorophenylthio)cyclododecan-1-one (4b-S). Electrochemical oxidation (2.1 F/mol) of di(4-fluorophenyl)disulfide (31.1 mg, 0.122 mmol), subsequent addition of the solution of cyclododecene (**2b**) (*E*/*Z* mixture, 33.3 mg, 0.200 mmol) in CH_2Cl_2 (0.5 mL), and treatment with Et_3N followed by flash chromatography (hexane/EtOAc 100:1) gave the title compound (54.5 mg, 88%); TLC R_f 0.66 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23–1.33 (m, 14 H), 1.51 (m, 1 H), 1.70 (m, 1 H), 1.83 (m, 1 H), 1.95 (m, 1 H), 2.57–2.70 (m, 2 H), 3.80 (dd, *J* = 3.2, 12.0 Hz, 1 H), 6.98 (m, 2 H), 7.33 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 22.5, 23.7, 24.0, 24.1, 24.4, 25.0, 25.4, 29.5, 36.5, 55.7, 116.2 (d, *J* = 21.8 Hz), 127.9 (d, *J* = 3.2 Hz), 134.9 (d, *J* = 7.9 Hz), 162.7 (d, *J* = 246.7 Hz), 208.0; HRMS (ESI) calcd for $C_{18}H_{29}NOFS$ [$M+NH_4^+$]: 326.1948, found: 326.1957.

1-(4-Fluorophenylthio)dodecan-2-one (4c-S). Electrochemical oxidation (2.1 F/mol) of di(4-fluorophenyl)disulfide (32.4 mg, 0.127 mmol), subsequent addition of the solution of 1-dodecene (**2c**) (32.7 mg, 0.194 mmol) in CH_2Cl_2 (0.5 mL), and treatment with Et_3N followed by flash chromatography (hexane/EtOAc 100:1) gave the title compound (48.3 mg, 80%); TLC R_f 0.63 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.2 Hz, 3 H), 1.24 (m, 14 H), 1.53 (m, 2 H), 2.56 (t, *J* = 7.2 Hz, 2 H), 3.61 (s, 2 H), 6.99 (m, 2 H), 7.36 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 23.8, 29.1, 29.27, 29.31, 29.4, 29.5, 31.9, 40.7, 44.9, 116.2 (d, *J* = 21.8 Hz), 129.6 (d, *J* = 3.1 Hz), 132.8 (d, *J* = 8.0 Hz), 162.2 (d, *J* = 245.9 Hz), 205.4; HRMS (APCI) calcd for $C_{18}H_{27}OFSNa$ [$M+Na^+$]: 333.1659, found: 333.1650.

2-(4-Fluorophenylthio)-1-phenylpropan-1-one (4d-S). Electrochemical oxidation (2.1 F/mol) of di(4-fluorophenyl)disulfide (33.4 mg, 0.131 mmol), subsequent addition of the solution of *trans*-β-methylstyrene (**2d**) (23.3 mg, 0.197 mmol) in CH_2Cl_2 (0.5 mL), and treatment with Et_3N followed by flash chromatography (hexane/EtOAc 10:1) gave the title compound (25.1 mg, 49%); TLC R_f 0.59 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (d, *J* = 6.8 Hz, 3 H), 4.56 (q, *J* = 6.8 Hz, 1 H), 6.97 (t, *J* = 8.8 Hz, 2 H), 7.28 (m, 2 H), 7.46 (t, *J* = 8.0 Hz, 2 H), 7.58 (m, 1 H), 7.95 (dd, *J* = 1.2, 8.0 Hz, 2 H). The spectra were in agreement with the literature.[13(b)]

1-(4-Fluorophenylthio)-1-phenylpropan-2-one (4d'-S). Isolated as above (14.3 mg, 28%); TLC R_f 0.48 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 3 H), 4.88 (s, 1 H), 6.93 (t, *J* = 8.8 Hz, 2 H), 7.26–7.31 (m, 7 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.5, 65.4, 116.1 (d, *J* = 21.8 Hz), 128.29 (d, *J* = 3.4 Hz), 128.33, 128.6, 128.9, 135.4, 135.7 (d, *J* = 8.4 Hz), 162.8 (d, *J* = 247.2 Hz), 202.9; HRMS (EI) calcd for $C_{15}H_{13}FOS$ [M^+]: 260.0671, found: 260.0677.

8-(4-Fluorophenylthio)-2-cycloocten-1-one (4e-S). Electrochemical oxidation (2.1 F/mol) of

di(4-fluorophenyl)disulfide (32.2 mg, 0.127 mmol), subsequent addition of the solution of 1,3-cycloocta-diene (**2e**) (21.5 mg, 0.199 mmol) in CH_2Cl_2 (0.5 mL), and treatment with Et_3N followed by flash chromatography (hexane/EtOAc 50:1 to 10:1) gave the title compound (33.5 mg, 67%); TLC R_f 0.51 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66–1.74 (m, 4 H), 2.04 (m, 2 H), 2.20 (m, 1 H), 2.48 (m, 1 H), 3.78 (dd, *J* = 4.8, 11.2 Hz, 1 H), 5.99 (dd, *J* = 1.6, 12.8 Hz, 1 H), 6.20 (dt, *J* = 4.8, 12.8 Hz, 1 H), 7.01 (m, 2 H), 7.42 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 26.8, 28.5, 30.2, 59.2, 116.2 (d, *J* = 21.8 Hz), 126.3, 128.2 (d, *J* = 3.2 Hz), 135.5 (d, *J* = 8.3 Hz), 139.1, 162.8 (d, *J* = 246.8 Hz), 202.4; HRMS (ESI) calcd for $C_{14}H_{16}OFS$ [M+H$^+$]: 251.0900, found: 251.0909.

2-(4-Fluorophenylthio)-2-cyclononen-1-one (4f-S). Electrochemical oxidation (2.1 F/mol) of di(4-fluorophenyl)disulfide (32.5 mg, 0.128 mmol), subsequent addition of the solution of 1,2-cyclononadiene (**2f**) (23.5 mg, 0.209 mmol) in CH_2Cl_2 (0.5 mL), and treatment with Et_3N followed by flash chromatography (hexane/EtOAc 100:1 to 50:1) gave the title compound (20.5 mg, 37%); TLC R_f 0.56 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (br s, 6 H), 1.83 (m, 2 H), 2.37 (m, 2 H), 2.59 (m, 2 H), 6.12 (t, *J* = 8.8 Hz, 1 H), 6.99 (t, *J* = 8.8 Hz, 2 H), 7.34 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.7, 24.8, 25.4, 26.3, 27.1, 40.0, 116.2 (d, *J* = 21.8 Hz), 128.3 (d, *J* = 3.5 Hz), 133.3 (d, *J* = 8.4 Hz), 137.0, 137.5, 162.4 (d, *J* = 246.0 Hz), 205.9; HRMS (APCI) calcd for $C_{15}H_{18}OFS$ [M+H$^+$]: 265.1057, found: 265.1056.

***N*-Tosyl-2-(4-fluorophenylthiomethyl)pyrrolidine (4g-S).** Electrochemical oxidation (2.1 F/mol) of di(4-fluorophenyl)disulfide (31.7 mg, 0.125 mmol), subsequent addition of the solution of *N*-tosyl-4-penten-1-amine (**2g**) (48.3 mg, 0.202 mmol) in CH_2Cl_2 (0.5 mL), and treatment with Et_3N followed by flash chromatography (hexane/EtOAc 10:1 to 5:1) and GPC gave the title compound (30.5 mg, 41%); TLC R_f 0.31 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (m, 1 H), 1.62 (m, 1 H), 1.82 (m, 2 H), 2.41 (s, 3 H), 2.76 (dd, *J* = 10.0, 13.2 Hz, 1 H), 3.10 (m, 1 H), 3.50 (m, 1 H), 3.56 (m, 1 H), 3.61 (m, 1 H), 7.06 (dd, *J* = 8.4, 8.4 Hz, 2 H), 7.25 (dd, *J* = 0.4, 8.4 Hz, 2 H), 7.45 (dd, *J* = 5.2, 8.8 Hz, 2 H), 7.52 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 23.7, 30.2, 39.5, 49.7, 58.9, 116.1 (d, *J* = 21.8 Hz), 127.4, 129.6, 130.1 (d, *J* = 3.2 Hz), 131.8 (d, *J* = 7.9 Hz), 133.7, 143.5, 161.7 (d, *J* = 244.3 Hz); HRMS (ESI) calcd for $C_{18}H_{20}FNO_2S_2$ [M+H$^+$]: 366.0992, found: 366.0983.

(3*R,4*S**,5*S**)-*N*-Tosyl-3-benzoyl-5-(4-fluorophenylthio)-4-phenylpiperidine (4h-S).** Electrochemical oxidation (2.1 F/mol) of di(4-fluorophenyl)disulfide (30.9 mg, 0.122 mmol), subsequent addition of the solution of dicinnamyltosylamine (**2h**) (76.6 mg, 0.190 mmol) in CH_2Cl_2 (0.5 mL), and treatment with Et_3N followed by flash chromatography (hexane/EtOAc 5:1) gave the title compound (65.1 mg, 63%); TLC R_f 0.24 (hexane/EtOAc 5:1): ^{1}H NMR (400

MHz, $CDCl_3$) δ 2.46 (s, 3 H), 2.50 (t, *J* = 12.0 Hz, 2 H), 2.97 (dd, *J* = 11.2, 11.2 Hz, 1 H), 3.46 (dt, *J* = 4.8, 11.6 Hz, 1 H), 3.98 (m, 1 H), 4.09 (dt, *J* = 4.0, 11.2 Hz, 1 H), 4.16 (m, 1 H), 6.93 (m, 2 H), 7.16 (m, 5 H), 7.32 (m, 4 H), 7.45 (m, 1 H), 7.60 (d, *J* = 8.4 Hz, 2 H), 7.66 (dd, *J* = 1.2, 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 49.1, 49.8, 50.27, 50.33, 52.1, 116.1 (d, *J* = 21.5 Hz), 127.4, 127.6, 127.9 (d, *J* = 2.9 Hz), 128.1, 128.5, 128.6, 129.9, 133.2, 133.6, 135.5, 135.6, 136.0, 139.3, 144.2, 162.7 (d, *J* = 247.0 Hz); HRMS (ESI) calcd for $C_{31}H_{29}FNO_3S_2$ [M+H$^+$]: 546.1567, found: 546.1549. The stereochemistry on the piperidine ring was analogized by that of **4h-Br**, which was determined by NOE analyses.

6-(Phenylseleno)decan-5-one (4a-Se). Electrochemical oxidation (2.1 F/mol) of diphenyldiselenide (37.3 mg, 0.120 mmol), and subsequent addition of a solution of (*Z*)-5-decene (**2a**) (27.3 mg, 0.195 mmol) in CH_2Cl_2 (0.5 mL), and treatment with Et_3N followed by flash chromatography (hexane/EtOAc 20:1) gave the title compound (36.4 mg, 60%). TLC R_f 0.62 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.8 Hz, 3 H), 0.89 (t, *J* = 6.8 Hz, 3 H), 1.30 (m, 5 H), 1.40 (m, 1 H), 1.55 (m, 2 H), 1.71 (m, 1 H), 1.83 (m, 1 H), 2.52 (m, 1 H), 2.60 (m, 1 H), 3.63 (t, *J* = 7.6 Hz, 1 H), 7.29 (m, 3 H), 7.50 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 13.9, 22.3, 22.4, 26.3, 30.1, 30.3, 40.2, 51.7, 127.5, 128.5, 129.1, 135.6, 206.6; HRMS (ESI) calcd for $C_{16}H_{25}OSe$ [M+H$^+$]: 313.1065, found: 313.1057.

2-(Phenylseleno)cyclododecan-1-one (4b-Se). Electrochemical oxidation (2.1 F/mol) of diphenyldiselenide (40.8 mg, 0.131 mmol), subsequent addition of the solution of cyclododecene (**2b**) (*E*/*Z* mixture, 32.6 mg, 0.196 mmol) in CH_2Cl_2 (0.5 mL), and treatment with Et_3N followed by flash chromatography (hexane/EtOAc 20:1) gave the title compound (59.9 mg, 91%); TLC R_f 0.62 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22–1.39 (m, 14 H), 1.57 (m, 1 H), 1.76 (m, 2 H), 2.10 (m, 1 H), 2.48 (m, 1 H), 2.81 (ddd, *J* = 3.2, 6.8, 14.4 Hz, 1 H), 4.00 (dd, *J* = 3.2, 13.2 Hz, 1 H), 7.26–7.32 (m, 3 H), 7.49–7.51 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 23.3, 24.31, 24.34, 24.74, 24.75, 25.38, 25.42, 30.3, 38.5, 48.5, 127.6, 128.5, 129.1, 135.3, 207.6; HRMS (ESI) calcd for $C_{18}H_{27}OSe$ [M+H$^+$]: 339.1222, found: 339.1229.

1-(Phenylseleno)dodecan-2-one (4c-Se). Electrochemical oxidation (2.1 F/mol) of diphenyldiselenide (38.8 mg, 0.124 mmol), subsequent addition of the solution of 1-dodecene (**2c**) (32.5 mg, 0.193 mmol) in CH_2Cl_2 (0.5 mL), and treatment with Et_3N followed by flash chromatography (hexane/EtOAc 100:1 to 50:1) gave the title compound (52.4 mg, 80%); TLC R_f 0.52 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.2 Hz, 3 H), 1.24 (m, 14 H), 1.53 (m, 2 H), 2.56 (t, *J* = 7.2 Hz, 2 H), 3.59 (s, 2 H), 7.28 (m, 3 H), 7.52 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 24.0, 29.1, 29.28, 29.31, 29.4, 29.5, 31.9, 36.0, 40.7, 127.8, 128.9, 129.3, 133.3, 206.0; HRMS (ESI) calcd for $C_{18}H_{29}OSe$ [M+H$^+$]: 341.1379, found:

341.1389.

1-(Phenylseleno)-1-phenylpropan-2-one (4d'-Se). Electrochemical oxidation (2.1 F/mol) of diphenyldiselenide (38.8 mg, 0.124 mmol), subsequent addition of the solution of *trans*-β-methylstyrene (**2d**) (23.5 mg, 0.199 mmol) in CH_2Cl_2 (0.5 mL), and treatment with Et_3N followed by flash chromatography (hexane/EtOAc 20:1) gave the title compound (36.0 mg, 63%); TLC R_f 0.55 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 3 H), 5.01 (s, 1 H), 7.20–7.33 (m, 8 H), 7.41 (d, J = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.0, 58.3, 127.9, 128.45, 128.48, 128.7, 128.8, 129.0, 135.5, 136.3, 203.1; HRMS (APCI) calcd for $C_{15}H_{15}OSe$ [M+H$^+$]: 291.0283, found: 291.0270.

8-(Phenylseleno)-2-cyclooctan-1-one (4e-Se). Electrochemical oxidation (2.1 F/mol) of diphenyldiselenide (38.3 mg, 0.123 mmol), subsequent addition of the solution of 1,3-cyclooctadiene (**2e**) (21.5 mg, 0.199 mmol) in CH_2Cl_2 (0.5 mL), and treatment with Et_3N followed by flash chromatography (hexane/EtOAc 10:1 to 5:1) gave the title compound (13.3 mg, 24%); TLC R_f 0.34 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 (m, 2 H), 1.88 (m, 3 H), 2.09 (m, 1 H), 2.48 (m, 1 H), 2.58 (m, 1 H), 4.14 (m, 1 H), 5.72 (ddd, J = 0.8, 2.0, 12.8 Hz, 1 H), 6.34 (dd, J = 4.8, 12.8 Hz, 1 H), 7.31 (m, 3 H), 7.56 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 27.2, 29.6, 43.0, 43.6, 127.7, 128.1, 128.5, 129.2, 134.9, 140.5, 207.5; HRMS (APCI) calcd for $C_{14}H_{16}OSe$ [M+H$^+$]: 281.0439, found: 281.0435.

2-(Phenylseleno)-2-cyclononen-1-one (4f-Se). Electrochemical oxidation (2.1 F/mol) of diphenyldiselenide (38.4 mg, 0.123 mmol), subsequent addition of the solution of 1,2-cyclononadiene (**2f**) (23.6 mg, 0.193 mmol) in CH_2Cl_2 (0.5 mL), and treatment with Et_3N followed by flash chromatography (hexane/EtOAc 20:1 to 10:1) gave the title compound (45.2 mg, 80%); TLC R_f 0.57 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (m, 6 H), 1.83 (m, 2 H), 2.38 (m, 2 H), 2.63 (m, 2 H), 6.15 (t, J = 4.8 Hz, 1 H), 7.28 (m, 3 H), 7.52 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 25.1, 25.9, 26.4, 28.1, 40.0, 127.9, 128.9, 129.3, 133.8, 134.5, 138.4, 206.0; HRMS (APCI) calcd for $C_{15}H_{19}OSe$ [M+H$^+$]: 295.0596, found: 295.0588.

***N*-Tosyl-2-(phenylselenomethyl)pyrrolidine (4g-Se).** Electrochemical oxidation (2.1 F/mol) of diphenyldiselenide (38.6 mg, 0.124 mmol), subsequent addition of the solution of *N*-tosyl-4-penten-1-amine (**2g**) (59.9 mg, 0.250 mmol) in CH_2Cl_2 (0.5 mL), and treatment with Et_3N followed by flash chromatography (hexane/EtOAc 5:1) gave the title compound (96.5 mg, 99%); TLC R_f 0.37 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (m, 1 H), 1.65 (m, 1 H), 1.80 (m, 2 H), 2.39 (s, 3 H), 2.83 (dd, J = 11.2, 12.8 Hz, 1 H), 3.12 (dt, J = 10.0, 7.2 Hz, 1 H), 3.48 (m, 1 H) 3.62 (m, 2 H), 7.22 (d, J = 8.2 Hz, 2 H), 7.31 (m, 3 H), 7.50 (d, J = 8.4 Hz, 2 H),

7.59 (dd, J = 1.2, 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 23.7, 30.9, 32.8, 49.8, 59.7, 126.8, 127.4, 129.1, 129.2, 129.5, 132.3, 133.7, 143.3; HRMS (ESI) calcd for $C_{18}H_{22}NO_2SSe$ [M+H$^+$]: 396.0531, found: 396.0522.

(3*R,4*S**,5*S**)-*N*-Tosyl-3-benzoyl-5-(phenylseleno)-4-phenylpiperidine (4h-Se).** Electrochemical oxidation (2.1 F/mol) of diphenyldiselenide (40.2 mg, 0.129 mmol), subsequent addition of the solution of dicinnamyltosylamine (**2h**) (80.3 mg, 0.199 mmol) in CH_2Cl_2 (0.5 mL), and treatment with Et_3N followed by washing with hexane/EtOAc/$CHCl_3$ gave the title compound (92.6 mg, 81%); TLC R_f 0.33 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3 H), 2.51 (t, J = 12.0 Hz, 1 H), 2.61 (t, J = 12.0 Hz, 1 H), 3.04 (t, J = 11.6 Hz, 1 H), 3.60 (dt, J = 4.4, 12.0 Hz, 1 H), 3.99 (m, 1 H), 4.08 (dt, J = 4.0, 11.2 Hz, 1 H), 4.19 (m, 1 H), 7.10 (m, 5 H), 7.20–7.34 (m, 9 H), 7.44 (m, 1 H), 7.57 (d, J = 8.4 Hz, 2 H), 7.64 (d, J = 7.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 44.1, 49.0, 50.1, 50.5, 52.7, 127.0, 127.3, 127.5, 127.9, 128.0, 128.1, 128.4, 128.5, 129.0, 129.8, 133.1, 133.4, 135.3, 135.9, 139.7, 144.0, 199.4; HRMS (ESI) calcd for $C_{31}H_{30}NO_3SSe$ [M+H$^+$]: 576.1106, found: 576.1094. The stereochemistry on the piperidine ring was analogized by that of **4h-Br**, which was determined by NOE analyses.

Comparison with other I$^+$ species.

The reaction with *N*-iodosuccinimide: To a round-bottomed flask *N*-iodosuccinimide (55.0 mg, 0.245 mmol), DMSO (1 mL), and CH_2Cl_2 (9.0 mL) were added, and the mixture was stirred at −78 ^{o}C. After the addition of cyclododecene (**2b**) (33.6 mg, 0.202 mmol), the mixture was stirred for 30 min at −78 ^{o}C and then stirred for 30 min at 0 ^{o}C. Then triethylamine (0.1 mL) was added, and the resulting mixture was allowed to be warmed to 25 ^{o}C, and stirred for additional 1 hour. The solution was collected and the solvent was removed under reduced pressure. Then, the residue was filtered through a short column (2 x 4) of silica gel using diethylether as an eluent. The ^{1}H NMR analysis of the crude compound indicated no generation of **4b-I** and 87% recovery of **2b**.

The reaction with I$^+$/MeCN: In the anodic chamber were placed iodine (36.8 mg, 0.145 mmol), Bu_4NBF_4 (980 mg, 3.0 mmol), and CH_3CN (10 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (30 μL, 0.34 mmol) and 0.3 M Bu_4NBF_4/CH_3CN (10 mL). The constant current electrolysis (8.0 mA) was carried out at 0 ^{o}C with magnetic stirring until 2.0 F/mol of electricity was consumed. The anodic solution was transferred to a solution of cyclododecene (**2b**) (33.4 mg, 0.201 mmol) in DMSO (1 mL) and CH_3CN (2 mL), and the solution was stirred for 30 min at 0 ^{o}C. Then triethylamine (0.1 mL) was added, and the resulting mixture was allowed to be warmed to 25 ^{o}C and stirred for additional 1 hour. The solution was collected and the solvent was removed under reduced pressure. Then, the residue was filtered

through a short column (2 x 4 cm) of silica gel to remove Bu_4NBF_4 by using hexane/EtOAc (1:1 v/v) as an eluent. The ^{1}H NMR analysis of the crude compound indicated the generation of **4b-I** in 37% yield.

The reaction with I^+/TMOF: In the anodic chamber were placed iodine (36.2 mg, 0.143 mmol), $LiClO_4$ (420 mg, 3.9 mmol), and trimethyl orthoformate (TMOF) (10 mL). In the cathodic chamber was placed 0.4 M $LiClO_4$/ TMOF (10 mL). The constant current electrolysis (8.0 mA) was carried out at 25 ^{o}C with magnetic stirring until 3.0 F/mol of electricity was consumed. The anodic solution was transferred to a solution of cyclododecene (**2b**) (33.4 mg, 0.201 mmol) in DMSO (1 mL) and TMOF (2 mL), and the solution was stirred for 30 min at 0 ^{o}C. Then triethylamine (0.1 mL) was added, and the resulting mixture was allowed to be warmed to 25 ^{o}C and stirred for additional 1 hour. The solution was collected and the solvent was removed under reduced pressure. Then, the residue was filtered through a short column (2 x 4 cm) of silica gel to remove Bu_4NBF_4 by using hexane/EtOAc (1:1 v/v) as an eluent. The ^{1}H NMR analysis of the crude compound indicated no generation of **4b-I** and 69% recovery of **2b**.

Comparison of thermal stability of 1-X. In the anodic chamber were placed the cation precursors (0.25 mmol of Bu_4NBr and Bu_4NI, 0.125 mmol of PhSSPh, ArSSAr, and PhSeSePh), Bu_4NBF_4 (980 mg, 3.0 mmol), DMSO (1 mL), and CH_2Cl_2 (9 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (60 μL for Br and I, 30 μL for SPh, SAr, and SePh) and 0.3 M Bu_4NBF_4/CH_2Cl_2 (10 mL). The constant current electrolysis (8.0 mA) was carried out at –78 ^{o}C with magnetic stirring until 2.1 F/mol of electricity was consumed. The solution was stirred at pre-determined second temperature (–78, –50, –20, and 0 ^{o}C) for 30 min, and then was stirred at –78 ^{o}C for 10 mon. To the anodic chamber was added a solution of cyclododecene (**2b**) (*E*/*Z* mixture, 80 mg, 0.5 mmol) in CH_2Cl_2 (0.5 mL), and to the cathodic chamber 0.5 mL of CH_2Cl_2 was added at –78 ^{o}C. The solution was stirred for 30 min at –78 ^{o}C, and then was stirred for 30 min at 0 ^{o}C. Then triethylamine (0.1 mL) was added to both the anodic and cathodic chambers, and the resulting mixture was allowed to be warmed to 25 ^{o}C and stirred for additional 1 hour. The solution in the anodic chambers was collected and the solvent was removed under reduced pressure. Then, the residue was filtered through a short column (2 x 4 cm) of silica gel to remove Bu_4NBF_4 by using hexane/EtOAc (1:1) as an eluent. After removal of the solvent under reduced pressure the crude product was analyzed by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. The results are summarized in Table S1.

2-(Phenylthio)cyclododecan-1-one (4b-S'). TLC R_f 0.66 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23–1.58 (m, 15 H), 1.75 (m, 1 H), 1.82 (m, 1 H), 2.00 (m, 1 H), 2.52 (ddd, *J* = 3.2, 6.4, 8.4 Hz, 1 H), 2.76 (ddd, *J* = 3.2, 11.6, 16.0 Hz, 1 H), 3.88 (dd, *J* = 3.6, 12.0 Hz, 1 H),

7.25 (m, 3 H), 7.33 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 22.3, 23.6, 24.0, 24.1, 25.3, 25.6, 29.6, 35.8, 55.6, 127.4, 129.0, 131.4, 133.5, 208.5; HRMS (ESI) calcd for $C_{16}H_{24}OS$ [M+H$^+$]: 291.1777, found: 291.1768.

Table S1. Residual rates (%) of **1-X** under several temperatures.

X	–78 °C	–50 °C	–20 °C	0 °C
Br	90	60	0	0
I	98	99	66	34
PhS	98	95	74	54
4-FC_6H_4-S	94	101	76	51
PhSe	101	103	88	66

Cartesian coordinates and energies of X^+ species.

The summary of the relative energies of I^+ species is shown in Table S2.

Table S2. Relative energies (kcal/mol) of S_n–I^+ species (S (stabilizing agent) = DMSO, MeCN, and TMOF, *n* =1–3). The basis of each energy is non-coordinated I^+ and *n* equivalent of S.

S	S–I^+	S_2–I^+	S_3–I^+
DMSO	-118.9	-155.0	-162.5
MeCN	-101.5	-133.1	-140.6
TMOF	—	-130.0	—

I^+ (C_1 symmetry) calculated at the RB3LYP/LANL2DZ level. Sum of electronic and zero-point Energies (hartree): −10.907403.

DMSO (C_s symmetry) calculated at the RB3LYP/6-31G(d) level. Sum of electronic and zero-point Energies (hartree): −553.107081.

Atom	X (Å)	Y (Å)	Z (Å)	Atom	X (Å)	Y (Å)	Z (Å)
O	-1.092935	1.109339	0.000000	H	0.211050	-0.241207	2.300310
S	0.257740	0.431076	0.000000	H	-0.624764	-1.442125	1.276083
C	0.257740	-0.801398	1.363339	H	1.177100	-1.394240	-1.331026
C	0.257740	-0.801398	-1.363339	H	0.211050	-0.241207	-2.300310
H	1.177100	-1.394240	1.331026	H	-0.624764	-1.442125	-1.276083

DMSO−I^+ (C_s symmetry) calculated at the level of RB3LYP/6-31G(d), and LANL2DZ (with ECP) for I. Sum of electronic and zero-point Energies (hartree): −564.203990; O−I bond length (Å): 2.09.

Atom	X (Å)	Y (Å)	Z (Å)	Atom	X (Å)	Y (Å)	Z (Å)
O	-0.326282	0.747064	0.000000	H	1.1406030	1.7396930	2.3140480
S	1.239174	1.212944	0.000000	H	2.2024270	2.8677690	-1.4167540
C	1.239174	2.347153	1.411328	H	0.4072480	3.0491140	-1.3166170
C	1.239174	2.347153	-1.411328	H	1.1406030	1.7396930	-2.3140480
H	0.407248	3.049114	1.316617	I	-0.7469280	-1.2992940	0.0000000
H	2.202427	2.867769	1.416754				

$DMSO_2$−I^+ (C_{2h} symmetry) calculated at the level ofRB3LYP/6-31G(d), and LANL2DZ (with ECP) for I. Sum of electronic and zero-point Energies: (hartree): −1117.368651; O−I bond length (Å): 2.27, 2.27.

Atom	X (Å)	Y (Å)	Z (Å)	Atom	X (Å)	Y (Å)	Z (Å)
O	0.623960	2.183709	0.000000	H	-0.1812950	3.7917810	-2.3065930
O	-0.623960	-2.183709	0.000000	H	-0.6232110	5.2600840	-1.3843410
S	-0.488266	3.304853	0.000000	H	1.0598210	4.6113100	-1.3020960
C	0.000000	4.360974	1.392301	H	0.1812950	-3.7917810	2.3065930
C	0.000000	4.360974	-1.392301	H	-1.0598210	-4.6113100	1.3020960
S	0.488266	-3.304853	0.000000	H	0.6232110	-5.2600840	1.3843410
C	0.000000	-4.360974	1.392301	H	0.1812950	-3.7917810	-2.3065930
C	0.000000	-4.360974	-1.392301	H	0.6232110	-5.2600840	-1.3843410
H	-0.181295	3.791781	2.306593	H	-1.0598210	-4.6113100	-1.3020960
H	1.059821	4.611310	1.302096	I	0.0000000	0.0000000	0.0000000
H	-0.623211	5.260084	1.384341				

$DMSO_3$−I^+ (C_1 symmetry) calculated at the level of RB3LYP/6-31G(d), and LANL2DZ (with ECP) for I. Sum of electronic and zero-point Energies (hartree): −1670.487625; O−I bond length (Å): 2.26, 2.28, 3.98.

Atom	X (Å)	Y (Å)	Z (Å)	Atom	X (Å)	Y (Å)	Z (Å)
O	2.740170	0.590856	-0.516028	H	-1.7904390	-2.4339900	-2.0731130
O	-1.732156	1.208326	0.058385	H	-1.9062290	-0.9452380	-1.0464400
O	0.058743	-3.026778	0.060088	H	-4.0343670	1.4386660	-1.7081610
S	-1.499204	-2.984877	0.222518	H	-4.3000220	3.2122380	-1.5524860
C	-1.883205	-1.868184	1.607495	H	-2.8110580	2.5922300	-2.3214750
C	-2.179483	-2.000044	-1.148960	H	-4.8543270	2.7807710	1.0571900

S	-2.681114	2.413362	0.058535	H	-3.7490380	1.8770490	2.1301320
C	-3.557124	2.409171	-1.544710	H	-4.5491730	1.0320490	0.7664370
C	-4.114060	1.976755	1.105221	H	4.1111720	3.5863640	0.8516350
S	2.622489	1.728354	0.573119	H	4.1911900	2.9019030	-0.8179520
C	4.134287	2.673823	0.249029	H	4.9756560	2.0462260	0.5498610
C	1.365765	2.861563	-0.083548	H	1.6260520	3.1372010	-1.1088580
H	-2.956660	-1.958305	1.802656	H	1.3191770	3.7433480	0.5630310
H	-1.621629	-0.834743	1.361360	H	0.4113100	2.3227950	-0.0554770
H	-1.326392	-2.235062	2.472948	I	1.4023730	-1.2291780	-0.2140510
H	-3.266886	-2.124227	-1.120070				

MeCN (C_{3v} symmetry) calculated at the RB3LYP/6-31G(d) level. Sum of electronic and zero-point Energies (hartree): −132.709287.

Atom	X (Å)	Y (Å)	Z (Å)	Atom	X (Å)	Y (Å)	Z (Å)
C	0.000000	0.000000	-1.180391	H	0.888632	-0.513052	-1.561798
H	0.000000	1.026104	-1.561798	C	0.000000	0.000000	0.280446
H	-0.888632	-0.513052	-1.561798	N	0.000000	0.000000	1.440723

MeCN−I^+ (C_{3v} symmetry) calculated at the level ofRB3LYP/6-31G(d), and LANL2DZ (with ECP) for I. Sum of electronic and zero-point Energies (hartree): −143.778452; N−I bond length (Å): 2.00.

Atom	X (Å)	Y (Å)	Z (Å)	Atom	X (Å)	Y (Å)	Z (Å)
C	0.000000	0.000000	-3.600705	C	0.000000	0.000000	-2.152881
H	0.000000	1.034055	-3.965429	N	0.000000	0.000000	-0.997037
H	-0.895518	-0.517027	-3.965429	I	0.000000	0.000000	1.007492
H	0.895518	-0.517027	-3.965429				

$MeCN_2$−I^+ (C_{3v} symmetry) calculated at the level of RB3LYP/6-31G(d), and LANL2DZ (with ECP) for I. Sum of electronic and zero-point Energies (hartree): −276.538116; N−I bond length (Å): 2.25, 2.25.

Atom	X (Å)	Y (Å)	Z (Å)	Atom	X (Å)	Y (Å)	Z (Å)
C	0.000000	0.000000	4.863019	N	0.000000	0.000000	-2.253764
H	0.000000	-1.031195	5.231339	C	0.000000	0.000000	-3.409292
H	-0.893041	0.515597	5.231339	C	0.000000	0.000000	-4.863122
H	0.893041	0.515597	5.231339	H	0.000000	1.031200	-5.231418
C	0.000000	0.000000	3.409215	H	0.893045	-0.515600	-5.231418
N	0.000000	0.000000	2.253687	H	-0.893045	-0.515600	-5.231418

I	0.000000	0.000000	0.000035

$MeCN_3$–I^+ (C_1 symmetry) calculated at the level of RB3LYP/6-31G(d), and LANL2DZ (with ECP) for I. Sum of electronic and zero-point Energies (hartree): −409.259403; N−I bond length (Å): 2.20, 2.30, 6.58 (N−H 2.13).

Atom	X (Å)	Y (Å)	Z (Å)	Atom	X (Å)	Y (Å)	Z (Å)
C	3.054548	-2.110950	-0.000428	H	-6.131031	2.103981	0.919879
H	3.196746	-2.727884	-0.894184	H	-6.092677	2.198607	-0.862821
H	3.196746	-2.728489	0.892912	H	-6.681318	0.716385	-0.059893
H	3.782193	-1.283459	-0.000149	C	6.046980	1.087429	-0.000216
C	1.711455	-1.566634	-0.000233	N	5.148074	0.355815	-0.000651
N	0.642985	-1.124178	-0.000083	C	7.178419	2.010411	0.000380
I	-1.397067	-0.290660	0.000259	H	8.027284	1.565261	-0.527814
N	-3.532621	0.573575	0.000491	H	6.903257	2.944652	-0.498753
C	-4.606702	1.000100	-0.000226	H	7.480998	2.234778	1.027884
C	-5.959149	1.537087	-0.000794				

TMOF (C_1 symmetry) calculated at the RB3LYP/6-31G(d) level. Sum of electronic and zero-point Energies (hartree): −383.934434.

Atom	X (Å)	Y (Å)	Z (Å)	Atom	X (Å)	Y (Å)	Z (Å)
C	-0.000225	0.000231	0.126185	C	0.745038	-2.237171	0.191530
H	-0.000074	0.000564	1.240739	H	0.708868	-2.243481	1.292188
O	-0.170478	-1.294587	-0.349520	H	0.436816	-3.216925	-0.179858
O	1.205985	0.499928	-0.350500	H	1.771262	-2.027996	-0.129494
O	-1.036553	0.794840	-0.349861	C	1.566466	1.763006	0.191798
C	-2.310564	0.473806	0.191631	H	2.570333	1.983838	-0.177461
H	-3.003979	1.233309	-0.176078	H	0.874830	2.549144	-0.130146
H	-2.645154	-0.517619	-0.132582	H	1.587689	1.734263	1.292485
H	-2.296518	0.504220	1.292389				

$TMOF_2$–I^+ (C_1 symmetry) calculated at the level of RB3LYP/6-31G(d), and LANL2DZ (with ECP) for I. Sum of electronic and zero-point Energies (hartree): −778.983508; O−I bond length (Å): 2.31, 2.31.

Atom	X (Å)	Y (Å)	Z (Å)	Atom	X (Å)	Y (Å)	Z (Å)
I	0.000070	0.154441	0.000604	H	4.412728	-1.206210	1.811684
C	3.210826	-0.042493	-0.287486	C	3.595004	2.197925	0.392486
C	-3.210806	-0.042479	0.286758	H	3.618237	2.747486	1.333109

H	4.062283	0.119678	-0.973139	H	4.596635	2.191805	-0.053672
H	-4.062536	0.119258	0.972173	H	2.883952	2.666716	-0.294574
O	-3.180973	0.862548	-0.727634	C	-2.009198	-0.609611	2.357757
O	-3.119363	-1.322031	-0.174822	H	-1.166677	-0.248648	2.945905
O	-2.017392	0.171860	1.126860	H	-2.945004	-0.410668	2.886519
O	3.182018	0.861242	0.728108	H	-1.910769	-1.671947	2.129988
O	2.017073	0.173455	-1.126633	C	-3.593938	2.198886	-0.390648
O	3.119013	-1.322599	0.172560	H	-2.883192	2.666760	0.297353
C	2.008114	-0.606150	-2.358722	H	-3.616572	2.749564	-1.330628
H	1.164832	-0.244733	-2.945499	H	-4.595815	2.192379	0.054951
H	2.943313	-0.405882	-2.888051	C	-4.271971	-1.785848	-0.899264
H	1.910447	-1.668873	-2.132436	H	-4.067248	-2.827434	-1.145455
C	4.271342	-1.787429	0.896801	H	-5.171557	-1.726788	-0.273338
H	4.066447	-2.829314	1.141598	H	-4.413612	-1.203463	-1.813369
H	5.171140	-1.727667	0.271247				

The summary of relative energies of DMSO−X^+ species is shown in Table S3.

Table S3. Relative energies (kcal/mol) of DMSO−X^+ species (X = Br, 4-FC_6H_4S, and PhSe).

	X^++DMSO	DMSO–X^+	$DMSO_2$–X^+	$DMSO_3$–X^+
Br	0	-157.7	-199.8	-213.2
4-FC_6H_4S	0	-45.8	-64.9	-77.5
PhSe	0	-56.4	-86.1	-100.9

Br^+ (C_1 symmetry) calculated at the RB3LYP/6-31G(d) level. Sum of electronic and zero-point Energies (hartree): −2571.151705.

DMSO−Br^+ (C_1 symmetry) calculated at the RB3LYP/6-31G(d) level. Sum of electronic and zero-point Energies (hartree): −3124.509966; O−Br bond length (Å): 1.90.

Atom	X (Å)	Y (Å)	Z (Å)	Atom	X (Å)	Y (Å)	Z (Å)
Br	1.699942	-0.014735	-0.026852	H	-2.654213	1.907703	-0.341043
O	-0.042550	-0.453085	0.583797	H	-0.959022	2.295304	0.073604
S	-1.233340	0.001477	-0.469556	H	-3.439668	-0.876222	-0.351689
C	-1.775089	1.583909	0.226296	H	-2.563138	-1.093408	1.212457
C	-2.493820	-1.155661	0.123696	H	-2.190704	-2.154125	-0.199035
H	-2.003932	1.468011	1.288081				

$DMSO_2$−Br^+ (C_1 symmetry) calculated at the RB3LYP/6-31G(d) level. Sum of electronic and zero-point Energies (hartree): −3677.684235; O−Br bond length (Å): 2.10, 2.10.

Atom	X (Å)	Y (Å)	Z (Å)	Atom	X (Å)	Y (Å)	Z (Å)
Br	-0.000005	-0.064544	0.000004	H	5.009257	1.501759	-0.378623
O	1.970529	-0.072210	0.732289	H	3.586937	-2.244650	-0.374222
O	-1.970541	-0.072336	-0.732312	H	5.039789	-1.262494	-0.730339
S	3.079065	0.076975	-0.391117	H	4.427243	-1.392231	0.962839
C	4.122874	1.412870	0.256214	H	-3.534795	2.331688	-0.204870
C	4.154459	-1.354582	-0.094458	H	-4.396099	1.191831	-1.290676
S	-3.079050	0.076968	0.391103	H	-5.009126	1.501915	0.378653
C	-4.122780	1.412930	-0.256222	H	-3.587090	-2.244620	0.374292
C	-4.154547	-1.354521	0.094493	H	-5.039875	-1.262348	0.730364
H	3.534967	2.331675	0.204804	H	-4.427327	-1.392187	-0.962804
H	4.396125	1.191780	1.290687				

$DMSO_3$−Br^+ (C_1 symmetry) calculated at the RB3LYP/6-31G(d) level. Sum of electronic and zero-point Energies (hartree): −4230.812706; O−Br bond length (Å): 2.08, 2.13, 3.39.

Atom	X (Å)	Y (Å)	Z (Å)	Atom	X (Å)	Y (Å)	Z (Å)
Br	-0.345800	-1.214563	-0.769416	H	-3.722700	1.366526	0.919850
O	1.761423	-0.888297	-0.789981	H	-3.330954	1.210239	-0.813623
O	0.072621	1.715554	0.875772	H	-1.998835	1.156954	0.413394
O	-2.398094	-1.563582	-0.804078	H	-0.780016	2.773375	-1.768604
S	-3.325284	-0.888345	0.281276	H	0.867254	3.197891	-2.349386
C	-2.585593	-1.248218	1.901312	H	0.450009	1.492047	-1.984933
C	-3.044894	0.903394	0.195616	H	0.673053	5.091062	-0.324724
S	0.871745	2.704382	0.019368	H	0.422040	4.617818	1.381301
C	0.285091	2.534016	-1.703891	H	-0.890512	4.363064	0.191440
C	0.192603	4.369507	0.342643	H	4.691310	-2.260518	0.750687
S	2.436806	-1.485080	0.513494	H	4.515047	-1.136759	-0.649396
C	4.071258	-1.972238	-0.103006	H	3.925052	-2.827555	-0.765761
C	2.859827	-0.034420	1.517033	H	3.536174	0.620036	0.961919
H	-3.214098	-0.781576	2.665031	H	3.319962	-0.380760	2.447260
H	-1.567284	-0.856760	1.937798	H	1.913408	0.480941	1.714068
H	-2.595527	-2.333269	2.025097				

ArS^+ (C_1 symmetry) calculated at the RB3LYP/6-31G(d) level. Sum of electronic and zero-point Energies (hartree): −728.660112.

Atom	X (Å)	Y (Å)	Z (Å)	Atom	X (Å)	Y (Å)	Z (Å)
C	1.081394	-1.255157	0.000012	H	1.673771	-2.164346	0.000016
C	1.743925	0.000002	-0.000052	H	1.673761	2.164357	0.000019
C	1.081396	1.255159	0.000014	H	-0.846811	2.185372	0.000099
C	-0.284156	1.257089	0.000065	H	-0.846814	-2.185371	0.000102
C	-1.031410	0.000003	0.000045	F	3.045649	-0.000002	-0.000040
C	-0.284153	-1.257092	0.000067	S	-2.681670	-0.000001	-0.000049

DMSO−SAr^+ (C_1 symmetry) calculated at the RB3LYP/6-31G(d) level. Sum of electronic and zero-point Energies (hartree): −1281.840215; O−S bond length (Å): 1.83.

Atom	X (Å)	Y (Å)	Z (Å)	Atom	X (Å)	Y (Å)	Z (Å)
O	-1.744262	-0.462263	-0.689055	C	0.919570	-0.761532	0.085264
S	-2.510424	0.602613	0.291755	C	1.736374	-0.853225	-1.065252
C	-4.134579	-0.169406	0.524061	C	1.371924	-0.041551	1.214661
C	-2.887248	1.891467	-0.923820	C	2.973741	-0.228395	-1.092740
H	-4.548249	-0.454098	-0.446095	H	1.392580	-1.421644	-1.923347
H	-4.780496	0.548535	1.039098	C	2.611915	0.579789	1.195035
H	-3.985218	-1.047899	1.156457	H	0.753910	0.007327	2.105678
H	-3.557965	2.614688	-0.450464	C	3.389776	0.477963	0.038941
H	-3.350258	1.436377	-1.802300	H	3.625372	-0.283739	-1.957939
H	-1.942629	2.371842	-1.186492	H	2.993108	1.129138	2.048931
S	-0.598692	-1.617449	0.140541	F	4.578996	1.073810	0.017251

$DMSO_2$−SAr^+ (C_1 symmetry) calculated at the RB3LYP/6-31G(d) level. Sum of electronic and zero-point Energies (hartree): −1834.977773; O−S bond length (Å): 2.07, 2.07.

Atom	X (Å)	Y (Å)	Z (Å)	Atom	X (Å)	Y (Å)	Z (Å)
O	-1.940879	-1.223438	-0.712967	H	5.209640	0.004231	-0.156288
O	1.940879	-1.223515	0.712740	H	3.267812	-3.441729	-0.703081
S	-3.081390	-1.093343	0.369548	H	4.850847	-2.633195	-0.900313
C	-4.305899	-0.037814	-0.458345	H	4.181324	-2.922980	0.750670
C	-3.944027	-2.690719	0.291068	S	-0.000030	-1.165206	-0.000128
S	3.081496	-1.093453	-0.369626	C	-0.000043	0.613081	-0.000038
C	4.305576	-0.037164	0.457935	C	0.098654	1.317815	-1.212142
C	3.944639	-2.690515	-0.290411	C	-0.098770	1.317693	1.212136
H	-3.864580	0.957473	-0.540453	C	0.092280	2.710255	-1.217140

H	-4.519577	-0.442294	-1.450571	H	0.168446	0.771914	-2.147568
H	-5.209941	0.003478	0.155916	C	-0.092439	2.710132	1.217270
H	-3.266902	-3.441550	0.703942	H	-0.168551	0.771695	2.147506
H	-4.850175	-2.633460	0.901065	C	-0.000086	3.382529	0.000098
H	-4.180768	-2.923650	-0.749895	H	0.161643	3.278272	-2.138825
H	3.863880	0.957990	0.539626	H	-0.161840	3.278054	2.139011
H	4.519355	-0.441172	1.450331	F	-0.000127	4.721426	0.000162

$DMSO_3$−SAr^+ (C_1 symmetry) calculated at the RB3LYP/6-31G(d) level. Sum of electronic and zero-point Energies (hartree): −2388.104919; O−S bond length (Å): 1.97, 2.29, 3.34.

Atom	X (Å)	Y (Å)	Z (Å)	Atom	X (Å)	Y (Å)	Z (Å)
O	-0.041192	1.695105	0.185224	H	5.737100	2.028134	0.919116
O	3.179741	-0.354162	-0.031578	H	5.945754	0.647602	-0.197287
O	-0.239925	-2.527429	-0.353045	H	5.509175	0.342242	1.510801
S	1.051870	-3.433265	-0.476876	H	-2.373916	4.324439	-0.667998
C	2.091855	-2.725241	-1.790127	H	-1.421744	4.089264	0.845444
C	2.091375	-3.114256	0.980352	H	-2.708121	2.925478	0.396097
S	3.627383	1.094392	0.180535	H	0.799194	4.359442	-0.418576
C	2.958836	1.626788	1.793229	H	0.014530	4.550705	-2.029024
C	5.388251	1.023264	0.663733	H	1.315825	3.343299	-1.802200
S	-0.743878	2.561363	-0.898868	S	-0.149325	-0.570365	-0.123502
C	-1.932602	3.593641	0.015934	C	-1.901351	-0.546561	0.114774
C	0.471567	3.847458	-1.326907	C	-2.766383	-0.565349	-0.993979
H	2.922960	-3.421224	-1.941926	C	-2.435776	-0.506847	1.415076
H	2.459361	-1.736280	-1.498964	C	-4.146048	-0.544872	-0.810807
H	1.476140	-2.690228	-2.691647	H	-2.352842	-0.606131	-1.996390
H	2.907903	-3.842603	0.946231	C	-3.812691	-0.474803	1.608520
H	1.467518	-3.307301	1.856037	H	-1.766604	-0.497813	2.269111
H	2.478030	-2.090204	0.960796	C	-4.644581	-0.497590	0.489514
H	3.202502	0.877936	2.552340	H	-4.835103	-0.567854	-1.648296
H	3.388361	2.597690	2.058634	H	-4.250969	-0.443925	2.600355
H	1.876813	1.713069	1.670362	F	-5.970263	-0.470182	0.671741

$PhSe^+$ (C_1 symmetry) calculated at the RB3LYP/6-31G(d) level. Sum of electronic and zero-point Energies (hartree): −2630.610551.

Atom	X (Å)	Y (Å)	Z (Å)	Atom	X (Å)	Y (Å)	Z (Å)
C	-2.114698	1.239031	-0.000133	H	-2.677957	2.166343	-0.000205

C	-2.797500	0.000000	-0.000135	H	-2.677955	-2.166344	-0.000059
C	-2.114702	-1.239029	-0.000050	H	-0.177520	-2.177774	0.000121
C	-0.740285	-1.249888	0.000046	H	-0.177508	2.177768	-0.000022
C	-0.006301	-0.000005	0.000042	H	-3.884715	0.000006	-0.000219
C	-0.740284	1.249889	-0.000037	Se	1.784655	0.000000	0.000059

DMSO−SePh$^+$ (C_1 symmetry) calculated at the RB3LYP/6-31G(d) level. Sum of electronic and zero-point Energies (hartree): −3183.807548; O−Se bond length (Å): 1.95.

Atom	X (Å)	Y (Å)	Z (Å)	Atom	X (Å)	Y (Å)	Z (Å)
O	-1.388634	0.134114	0.809222	C	2.188259	0.151270	1.129819
S	-2.112793	-0.817644	-0.290433	C	1.811405	-0.241477	-1.254513
C	-3.578792	0.138273	-0.764371	C	3.352650	-0.606476	1.063786
C	-2.826722	-2.054787	0.823146	H	1.874784	0.610601	2.061705
H	-4.136102	0.430445	0.128532	C	2.985758	-0.986465	-1.311716
H	-4.187218	-0.478855	-1.432394	H	1.211137	-0.083534	-2.144887
H	-3.218530	1.018354	-1.303171	C	3.749801	-1.170899	-0.154376
H	-3.486554	-2.698804	0.234309	H	3.957707	-0.748852	1.953743
H	-3.373293	-1.550312	1.623145	H	3.307573	-1.420203	-2.253396
H	-1.997555	-2.638558	1.228111	H	4.665888	-1.752279	-0.203061
C	1.411108	0.328060	-0.030840	Se	-0.125437	1.411071	0.037497

DMSO$_2$−SePh$^+$ (C_1 symmetry) calculated at the RB3LYP/6-31G(d) level. Sum of electronic and zero-point Energies (hartree): −3736.961937; O−Se bond length (Å): 2.14, 2.14.

Atom	X (Å)	Y (Å)	Z (Å)	Atom	X (Å)	Y (Å)	Z (Å)
O	0.000000	2.141970	0.907452	H	-1.924733	-4.854473	-0.460828
O	0.000000	-2.141970	0.907452	H	-1.951231	-2.843988	2.993642
S	1.413657	2.800117	0.677359	H	-2.682629	-4.231109	2.134199
C	1.023611	4.244561	-0.350304	H	-0.925414	-4.245088	2.546266
C	1.777997	3.627749	2.252989	C	0.000000	0.000000	-1.021237
S	-1.413657	-2.800117	0.677359	C	-1.144243	0.413402	-1.715775
C	-1.023611	-4.244561	-0.350304	C	1.144243	-0.413402	-1.715775
C	-1.777997	-3.627749	2.252989	C	-1.137623	0.419447	-3.111117
H	0.708353	3.864087	-1.324071	H	-2.022155	0.730365	-1.161660
H	0.214972	4.813655	0.114706	C	1.137623	-0.419447	-3.111117
H	1.924733	4.854473	-0.460828	H	2.022155	-0.730365	-1.161660
H	1.951231	2.843988	2.993642	C	0.000000	0.000000	-3.806908
H	2.682629	4.231109	2.134199	H	-2.021136	0.742768	-3.654034

H	0.925414	4.245088	2.546266	H	2.021136	-0.742768	-3.654034
H	-0.708353	-3.864087	-1.324071	Se	0.000000	0.000000	0.893568
H	-0.214972	-4.813655	0.114706	H	0.000000	0.000000	-4.893130

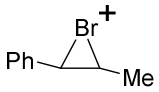
$DMSO_3$−$SePh^+$ (C_1 symmetry) calculated at the RB3LYP/6-31G(d) level. Sum of electronic and zero-point Energies (hartree): −4290.092563; O−Se bond length (Å): 2.12, 2.20, 3.15.

Atom	X (Å)	Y (Å)	Z (Å)	Atom	X (Å)	Y (Å)	Z (Å)
O	-0.291423	1.796569	0.253061	H	5.178846	2.017923	1.417911
O	2.837834	-0.148379	-0.301714	H	5.427033	1.310480	-0.206581
O	-0.410837	-2.503925	-0.116769	H	5.246657	0.230561	1.208193
S	0.755527	-3.354589	-0.734042	H	-2.374244	3.830483	-1.902152
C	1.387213	-2.440818	-2.178914	H	-2.289390	3.787114	-0.100039
C	2.175941	-3.183506	0.387640	H	-2.894057	2.366440	-1.010017
S	3.134683	1.145681	0.460801	H	0.164716	4.553109	-0.059386
C	2.599502	0.867224	2.185838	H	0.277338	4.654020	-1.856462
C	4.935514	1.178271	0.759956	H	1.500588	3.730528	-0.927609
S	-0.521770	2.504662	-1.130356	C	-2.160013	-0.440867	0.416887
C	-2.196390	3.206651	-1.021240	C	-3.068914	-0.652534	-0.628189
C	0.451535	4.030400	-0.975057	C	-2.621667	-0.256168	1.724846
H	2.154806	-3.066757	-2.643360	C	-4.438343	-0.675362	-0.362343
H	1.799992	-1.475568	-1.875770	H	-2.704394	-0.812984	-1.638516
H	0.547158	-2.318714	-2.866063	C	-3.992287	-0.268559	1.984090
H	2.957887	-3.862074	0.032750	H	-1.912712	-0.105500	2.532677
H	1.829761	-3.509694	1.371297	C	-4.899128	-0.478217	0.942470
H	2.528797	-2.146908	0.398638	H	-5.143604	-0.849376	-1.169982
H	3.177807	0.052152	2.630100	H	-4.351387	-0.124450	2.998941
H	2.719209	1.788121	2.763350	Se	-0.277608	-0.392502	0.058767
H	1.546037	0.585955	2.121170	H	-5.965573	-0.495074	1.147848

Cartesian coordinate, bond indexes and atomic charges of onium ions.

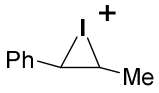
The summary of NBO bond indexes and atomic charges of the onium ions generated from DMSO−X^+ species with *trans*-β-methylstyrene (**2d**) is shown in Table S4 and S5.

Bromonium ion generated from 1-Br with 2d (C_1 symmetry) calculated at the RB3LYP/6-311++G(2df,2pd) level.



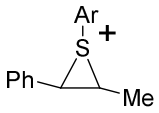
Atom	X (Å)	Y (Å)	Z (Å)	Atom	X (Å)	Y (Å)	Z (Å)
C	1.299107	0.878071	0.494785	H	1.045427	0.722077	1.540927
C	0.168335	0.764337	-0.442899	H	0.402360	1.048569	-1.468364
C	-1.147410	0.363431	-0.175171	H	3.165471	1.880516	0.872241
C	2.261988	2.028636	0.275848	H	1.785485	2.961267	0.602196
Br	2.097155	-0.868529	-0.125945	H	2.546743	2.126228	-0.775368
C	-2.071722	0.344853	-1.266817	H	-1.721940	0.608392	-2.261004
C	-3.394101	0.001402	-1.058651	H	-4.096592	-0.008032	-1.885201
C	-3.820872	-0.339760	0.234032	H	-4.859516	-0.612945	0.397997
C	-2.930037	-0.337130	1.324357	H	-3.285737	-0.607410	2.312991
C	-1.608402	0.008771	1.131130	H	-0.923431	0.004173	1.971980

Iodonium ion generated from 1-I with 2d (C_1 symmetry) calculated at the level of RB3LYP/6-311++G(2df,2pd), and SDB-cc-pVTZ (with ECP) for I.



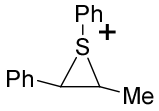
Atom	X (Å)	Y (Å)	Z (Å)	Atom	X (Å)	Y (Å)	Z (Å)
C	-0.819198	1.278843	-0.390579	H	-0.553392	1.261732	-1.444517
C	0.243219	0.879481	0.538116	H	0.024053	1.055326	1.590142
C	1.531778	0.397154	0.222213	H	-2.576691	2.525292	-0.609047
C	-1.683416	2.467672	0.017130	H	-1.100793	3.386474	-0.128145
I	-1.876078	-0.676125	0.000201	H	-1.988591	2.404399	1.065138
C	2.414262	0.096047	1.303982	H	2.060005	0.208008	2.322699
C	3.706992	-0.331915	1.056605	H	4.374654	-0.556285	1.878162
C	4.148033	-0.474186	-0.267351	H	5.160134	-0.808849	-0.461578
C	3.294587	-0.187407	-1.348847	H	3.655466	-0.301486	-2.362840
C	2.001433	0.241008	-1.115840	H	1.351136	0.459854	-1.953267

Thiiranium ion generated from 1-S (Ar = 4-FC$_6$H$_4$) with 2d (C_1 symmetry) calculated at the RB3LYP/ 6-311++G(2df,2pd) level.



Atom	X (Å)	Y (Å)	Z (Å)	Atom	X (Å)	Y (Å)	Z (Å)
C	1.425091	-1.983854	0.616510	H	0.843328	-1.669393	1.477706
C	2.064694	-0.917442	-0.140605	H	2.792693	-1.246626	-0.876983
C	1.949098	0.494015	0.050118	H	2.937857	-3.139807	1.590866
C	2.172295	-3.284714	0.823711	H	1.496092	-4.071322	1.160087
S	0.259883	-2.063212	-0.892544	H	2.669923	-3.623142	-0.087524
C	2.657574	1.344552	-0.833542	H	3.234096	0.910855	-1.644274
C	2.627117	2.717403	-0.664246	H	3.178485	3.361308	-1.339382
C	1.887845	3.269586	0.385978	H	1.868775	4.345278	0.522729
C	1.178980	2.447259	1.266701	H	0.616184	2.885815	2.082477
C	1.203562	1.072417	1.104449	H	0.660237	0.448684	1.803514
C	-1.088020	-0.990579	-0.466261	H	-0.753253	0.302674	-2.166663
C	-1.384290	0.087031	-1.312524	H	-2.756144	1.712889	-1.699000
C	-2.498257	0.877067	-1.059913	H	-3.687969	-0.698723	1.716973
C	-3.297080	0.577753	0.037212	H	-1.714368	-2.142645	1.259329
C	-3.024459	-0.492023	0.885864	I	-4.365386	1.337505	0.284349
C	-1.916745	-1.285472	0.626834				

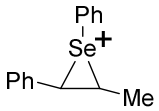
Thiiranium ion generated from 1-S' (Ar = Ph) with 2d (C_1 symmetry) calculated at the RB3LYP/ 6-311++G(2df,2pd) level.



Atom	X (Å)	Y (Å)	Z (Å)	Atom	X (Å)	Y (Å)	Z (Å)
C	-0.018701	2.224815	0.579549	H	0.307242	1.680976	1.464325
C	-1.097365	1.606122	-0.186855	H	-1.551067	2.245033	-0.942505
C	-1.726139	0.336522	0.029396	H	-0.752183	4.011074	1.503772
C	-0.010143	3.732835	0.746995	H	0.971559	4.078714	1.080669
S	1.023532	1.655266	-0.903464	H	-0.264168	4.248244	-0.184683
C	-2.769450	-0.042728	-0.852851	H	-3.033837	0.612764	-1.678411
C	-3.455805	-1.232441	-0.662213	H	-4.259020	-1.511571	-1.336456
C	-3.110276	-2.068778	0.406576	H	-3.650654	-2.998388	0.559240
C	-2.078024	-1.714370	1.284293	H	-1.822339	-2.366723	2.113038

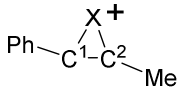
C	-1.387545	-0.524510	1.102240	H	-0.597528	-0.257926	1.795775
C	1.654780	0.063000	-0.420409	H	0.756676	-0.924312	-2.123891
C	1.392942	-1.036187	-1.251615	H	1.773627	-3.124694	-1.589654
C	1.967157	-2.270505	-0.948274	H	3.234161	-3.367766	0.403995
C	2.787406	-2.405336	0.173616	H	3.696270	-1.410060	1.860804
C	3.046410	-1.304745	0.997540	H	2.715476	0.798620	1.323470
C	2.487966	-0.063401	0.703003				

Seleniranium ion generated from 1-Se with 2d (C_1 symmetry) calculated at the RB3LYP/6-311++G(2df,2pd) level.



Atom	X (Å)	Y (Å)	Z (Å)	Atom	X (Å)	Y (Å)	Z (Å)
C	-0.365277	-1.987558	0.909255	H	-0.503378	-1.299077	1.740112
C	0.762717	-1.723092	0.025389	H	1.016161	-2.531956	-0.658060
C	1.728536	-0.652334	0.114895	H	-0.150268	-3.828890	1.973565
C	-0.792653	-3.412345	1.188437	H	-1.827611	-3.445373	1.538054
Se	-1.320169	-1.212683	-0.729743	H	-0.701576	-4.051418	0.304276
C	2.787484	-0.639456	-0.822508	H	2.820380	-1.396233	-1.602124
C	3.783630	0.324564	-0.749160	H	4.595631	0.321836	-1.469268
C	3.740122	1.293015	0.260074	H	4.522313	2.043777	0.322156
C	2.698798	1.294893	1.194830	H	2.675013	2.043431	1.980408
C	1.698003	0.333810	1.126508	H	0.903237	0.344198	1.864645
C	-1.420030	0.638895	-0.281375	H	-0.189594	1.232914	-1.957541
C	-0.787815	1.568207	-1.116249	H	-0.457681	3.659072	-1.493475
C	-0.940896	2.929158	-0.851447	H	-1.835536	4.408869	0.431590
C	-1.715858	3.348227	0.232296	H	-2.961180	2.743201	1.890189
C	-2.349251	2.412298	1.056720	H	-2.720723	0.318227	1.419948
C	-2.210750	1.049825	0.800130				

Table S4. The NBO bond indexes of the optimized structure for onium ions (C_1 symmetry) calculated at the level of RB3LYP/6-311++G(2df,2pd), and SDB-cc-pVTZ(with ECP) for I.



X	Br	I	PhS	ArS	PhSe
C1–X	0.222	0.287	0.493	0.468	0.492
C2–X	0.890	0.825	0.847	0.842	0.794
C1–C2	1.095	1.146	1.102	1.107	1.145

Table S5. The atomic charges of the optimized structure for onium ions (C_1 symmetry) calculated at the level of RB3LYP/6-311++G(2df,2pd), and SDB-cc-pVTZ(with ECP) for I.

X	Br	I	PhS	ArS	PhSe
C1	0.103	0.044	-0.025	-0.016	-0.061
C2	-0.264	-0.330	-0.297	-0.299	-0.307
X	0.175	0.355	0.536	0.526	0.661

References

(1) For Br and I, see: (a) Neilson, A. H., Ed. Organic Bromine and Iodine Compounds. In *The Handbook of Environmental Chemistry Part 3R*; Springer: Berlin, Heidelberg, 2003. For S and Se, see: (b) Schmidt, M., Siebert, W., Bagnall, K. W., Eds. *The Chemistry of Sulphur, Selenium, Tellurium, and Polonium*; Pergamon Press: Oxford, 1975.

(2) (a) Tanuwidjaja, J.; Ng, S.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 12084. (b) Zhou, L.; Tan, C. K.; Jiang, X.; Chen, F.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 15474. (c) Moriyama, K.; Izumisawa, Y.; Togo, H. *J. Org. Chem.* **2010**, *76*, 7249. (d) Snyder, S. A.; Treitler, D. S.; Brucks, A. P.; Sattler, W. *J. Am. Chem. Soc.* **2011**, *133*, 15898. (e) Mori, K.; Ichikawa, Y.; Kobayashi, M.; Shibata, Y.; Yamanaka, M.; Akiyama, T. *J. Am. Chem. Soc.* **2013**, *135*, 3964. (f) Denmark, S. E.; Jaunet, A. *J. Am. Chem. Soc.* **2013**, *135*, 6419.

(3) (a) Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527. (b) Sperry, J. B.; Wright, D. L. *Chem. Soc. Rev.* **2006**, *35*, 605. (c) Yoshida, J.; Kataoka, K.; Horcajada, R.; Nagaki, A. *Chem. Rev.* **2008**, *108*, 2265.

(4) Recent examples: (a) Bours, J.; Morton, M.; Fry, A. J. *Tetrahedron Lett.* **2012**, *53*, 1015. (b) Zeng, C.-c.; Zhang, N.-t.; Lam, C. M.; Little, R. D. *Org. Lett.* **2012**, *14*, 1314. (c) Dai, J.-J.; Huang, Y.-B.; Fang, C.; Guo, Q.-X.; Fu, Y. *ChemSusChem* **2012**, *5*, 617. (d) Kirste, A.; Elsler, B.; Schnakenburg, G.; Waldvogel, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 3571. (e)

Ishiguro, Y.; Inagi, S.; Fuchigami, T. *J. Am. Chem. Soc.* **2012**, *134*, 4034. (f) Finney, E. E.; Ogawa, K. A.; Boydston, A. J. *J. Am. Chem. Soc.* **2012**, *134*, 12374. (g) Sumi, K.; Saitoh, T.; Natsui, K.; Yamamoto, T.; Atobe, M.; Einaga, Y.; Nishiyama, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 5443. (h) Shida, N.; Ishiguro, Y.; Atobe, M.; Fuchigami, T.; Inagi, S. *ACS Macro Lett.* **2012**, *1*, 656. (i) Morofuji, T.; Shimizu, A.; Yoshida, J. *J. Am. Chem. Soc.* **2013**, *135*, 5000. (j) Yamaguchi, Y.; Okada, Y.; Chiba, K. *J. Org. Chem.* **2013**, *78*, 2826.

(5) Selected examples: (a) Yoshida, J.; Suga, S.; Suzuki, S.; Kinomura, N.; Yamamoto, A.; Fujiwara, K. *J. Am. Chem. Soc.* **1999**, *121*, 9546. (b) Suga, S.; Suzuki, S.; Yamamoto, A.; Yoshida, J. *J. Am. Chem. Soc.* **2000**, *122*, 10244. (c) Yoshida, J.; Suga, S. *Chem.−Eur. J.* **2002**, *8*, 2650. (d) Nokami, T.; Ohata, K.; Inoue, M.; Tsuyama, H.; Shibuya, A.: Soga, K.; Okajima, M.; Suga, S.; Yoshida, J. *J. Am. Chem. Soc.* **2008**, *130*, 10864. (e) Okajima, M.; Soga, K.; Watanabe, T.; Terao, K.; Nokami, T.; Suga, S.; Yoshida, J. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 594: For an example of radical cation pools, see: (f) Morofuji, T.; Shimizu, A.; Yoshida, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 7259.

(6) For reviews of oxidative generation of heteroatom cations by chemical oxidants, see: (a) Eissen, M.; Lenoir, D. *Chem.−Eur. J.* 2008, 14, 9830. (b) Podgorsek, A.; Zupan, M.; Iskra, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 842.

(7) Reversible generation of Br^+ cation in equilibrium has been reported: Derbyshire, D. H.; Waters, W. A. *Nature* **1949**, *164*, 446.

(8) Chemistry of carbocations and onium ions: (a) Olah, G. A.; Prakash, G. K. S. *Carbocation Chemistry*; Wiley-Interscience: Hoboken, 2004. (b) Laali, K. K., Ed. *Recent Developments in Carbocation and Onium Ion Chemistry*; ACS Symposium Series 965; American Chemical Society: Washington, DC, 2007.

(9) (a) Miller, L. L.; Kujawa, E. P.; Campbell, C. B. *J. Am. Chem. Soc.* **1970**, *92*, 2821. (b) Miller, L. L.; Watkins, B. F. *J. Am. Chem. Soc.* **1976**, *98*, 1515.

(10) The example of anodic oxidation to generate Br^+ with CH_3CN in the presence of nucleophiles: (a) Becker, J. Y.; Zemach, D. *J. Chem. Soc., Perkin Trans. 2* **1981**, 336: The example of Cl^+: (b) So, Y.-H. *J. Org. Chem.* **1985**, *50*, 5895: The example of I^+ with trifluoroacetic acid in the presence of nucleophiles: (c) Lines, R.; Parker, V. D. *Acta Chem. Scand.* **1980**, *B34*, 47.

(11) Midorikawa, K.; Suga, S.; Yoshida, J. *Chem. Commun.* **2006**, 3794.

(12) Shono, T.; Matsumura, Y.; Katoh, S.; Ikeda, K.; Kamada, T. *Tetrahedron Lett.* **1989**, *30*, 1649.

(13) Selected examples: (a) Suga, S.; Matsumoto, K.; Ueoka, K.; Yoshida, J. *J. Am. Chem. Soc.* **2006**, *128*, 7710. (b) Matsumoto, K.; Kozuki, Y.; Ashikari, Y.; Suga, S.; Kashimura, S.; Yoshida, J. *Tetrahedron Lett.* **2012**, *53*, 1916. (c) Matsumoto, K.; Sanada, T.; Shimazaki,

H.; Shimada, K.; Hagiwara, S.; Fujie, S.; Ashikari, Y.; Suga, S.; Kashimura, S.; Yoshida, J. *Asian J. Org. Chem.* **2013**, *2*, 325. and references cited therein.

(14) (a) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165. (b) Kornblum, N.; Powers, J. W.; Anderson, G. J.; Jones, W. J.; Larson, H. O.; Levand, O.; Weaver, W. M. *J. Am. Chem. Soc.* **1957**, *79*, 6562. (c) Phan, T. B.; Nolte, C.; Kobayashi, S.; Ofial, A. R.; Mayr, H. *J. Am. Chem. Soc.* **2009**, *131*, 11392.

(15) (a) Ashikari, Y.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2011**, *133*, 11840. (b) Ashikari, Y.; Nokami, T.; Yoshida, J. *Org. Biomol. Chem.* **2013**, *11*, 3322.

(16) (a) Schmidt, B. *Pure Appl. Chem.* **2006**, *78*, 469. (b) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861. (c) Yoshida, J.; Saito, K.; Nokami, T.; Nagaki, A. *Synlett* **2011**, 1189.

(17) Recent examples: (a) Suga, S.; Yamada, D.; Yoshida, J. *Chem. Lett.* **2010**, *39*, 404. (b) Kim, H.; Nagaki, A.; Yoshida, J. *Nat. Commun.* **2011**, *2*, 264. (c) Fuchibe, K.; Jyono, H.; Fujiwara, M.; Kudo, T.; Yokota, M.; Ichikawa, J. *Chem.−Eur. J.* **2011**, *17*, 12175. (d) Mitamura, Y.; Yorimitsu, H.; Oshima, K.; Osuka, A. *Chem. Sci.* **2011**, *2*, 2017. (e) Asano, K.; Matsubara, S. *Org. Lett.* **2012**, *14*, 1620. (f) Murata, T.; Murai, M.; Ikeda, Y.; Miki, K.; Ohe, K. *Org. Lett.* **2012**, *14*, 2296. (g) Fuse, S.; Mifune, Y.; Tanabe, N.; Takahashi, T. *Org. Biomol. Chem.* **2012**, *10*, 5205. (h) Mitsudo, K.; Kamimoto, N.; Murakami, H.; Mandai, H.; Wakamiya, A.; Murata, Y.; Suga, S. *Org. Biomol. Chem.* **2012**, *10*, 9562.

(18) Cationic halogen−DMSO complexes in the troposphere have been only predicted by computational calculation; see: Sayin, H.; McKee, M. L. *J. Phys. Chem. A.* **2004**, *108*, 7613.

(19) The DFT calculations (B3LYP/6-31G(d), and LANL2DZ (with ECP) for I) were performed with the Gaussian 09 program.

(20) The example of computational calculation of stabilized halogen cations with bases: Alcamí, M.; Mó, O.; Yáñez, M.; Abboud, J.-L. M. *J. Phys. Org. Chem.* **1991**, *4*, 177.

(21) The detailed results are in the supporting information section and summarized in Table S2. The calculation results of other DMSO−X^+ species are also described in the supporting information section and summarized in Table S3.

(22) Yamaguchi, K. *J. Mass Spectrom.* **2003**, *38*, 473.

(23) (a) Tamao, K.; Yamaguchi S. *J. Organomet. Chem.* **2000**, *611*, 3. (b) Oestreich, M.; Hartmann, E.; Mewald, M. *Chem. Rev.* **2012**, *113*, 402; and references cited therein.

(24) (a) Yadav, J. S.; Reddy, B. V. S.; Singh, A. P.; Basak, A. K. *Tetrahedron Lett.* **2008**, *49*, 5880. (b) Moorthy, J. N.; Senapati, K.; Singhal, N. *Tetrahedron Lett.* **2009**, *50*, 2493.

(25) Boeckman, Jr., R. K.; Shao, P.; Mullins, J. J. *Org. Synth.* **2000**, *77*, 141.

(26) Kende, A. S. *Org. React.* **1960**, *11*, 261.

(27) Ocampo, R.; Dolbier, W. R. *Tetrahedron* **2004**, *60*, 9325.

(28) (a) Boryzka, S.; Elothmani, D.; Do, Q. T.; Simonet, J.; Guillanton, G. L. *J. Electrochem. Soc.* **1996**, *143*, 4027. (b) Do, Q. T.; Elothmani, D.; Simonet, J.; Guillanton, G. L. *Electrochim. Acta* **2005**, *50*, 4792.

(29) Niyomura, O.; Cox, M.; Wirth, T. *Synlett* **2006**, *2*, 251.

(30) Some of the intermediates of Pummerer rearrangement reaction have similar conformation such as TfO−S^+R_2 generated from a disulfide and Tf_2O, although they act as sulfonium ions, see: Murakami, K.; Imoto, J.; Matsubara, H.; Yoshida, S.; Yorimitsu, H.; Oshima, K. *Chem.−Eur. J.* **2013**, *19*, 5625 and reference cited therein.

(31) (a) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485. (b) Clive, D. L. J. *Tetrahedron* **1978**, 34, 1049.

(32) Pauling electronegativity; Shriver D. F.; Atkins, P. W.; Overton, T. L.; Rourke, J. P.; Weller, M. T.; Armstrong, F. A. *Inorganic Chemistry, 4th Edition*; Oxford University Press: Oxford, 2006.

(33) The thermal stability of **1-S** (4-$FC_6H_4S^+$**)** was quite similar to that of PhS^+ indicating that the nature of the substituent on the phenyl does not affect the stability significantly. The results are summarized in Table S1.

(34) Examples of lower regioselectivity for nucleophilic addition to bromonium ions; (a) Barton, D. H. R.; Poyser, J. P.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1* **1972**, *1*, 53. (b) Masuda, H.; Takase, K.; Nishio, M.; Hasegawa, A.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* **1994**, *59*, 5550.

(35) (a) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735 For a comparison of cationic species with different levels of basis sets, see: (b) Noronha, L. A.; Judson, T. J. L.; Dias, J. F.; Santos, L. S.; Eberlin, M. N.; Mota, C. J. A. *J. Org. Chem.* **2006**, *71*, 2625. (c) Schneider, T. F.; Werz, D. B. *Org. Lett.* **2010**, *12*, 4844.

(36) The DFT calculations at the lebel of B3LYP/6-311++G(2df,2pd) and SDB-cc-pVTZ (with ECP) for I were performed with the Gaussian 09 program. The results are summarized in Table S4 and S5 in the supporting section.

(37) (a) Ray, D. G., III; Koser, G. F. *J. Am. Chem. Soc.* **1990**, *112*, 5672. (b) Ashikari, Y.; Nokami, T.; Yoshida, J. *Org. Lett.* **2012**, *14*, 938; (Chapter 3).

(38) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435.

(39) Cyclizations with a similar mechanism: Matsumoto, K.; Fujie, S.; Suga,S.; Nokami, T.; Yoshida, J. *Chem. Commun.* **2009**, 5448.

(40) For recent examples of heteroatom initiated polyene cyclization, see: (a) Sakakura, A.; Ukai, K.; Ishihara, K. *Nature* **2007**, *445*, 900. (b) Snyder, S. A.; Treitler, D. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 7899. (c) Moore, J. T.; Soldi, C.; Fettinger, J. C.; Shaw, J. T. *Chem. Sci.* **2013**, *4*, 292.

(41) Gaussian 09, Revision A.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.;

Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, **2009**.

(42) Shea, K. J.; Kim, J.-S. *J. Am. Chem. Soc.* **1992**, *114*, 3044.

(43) Fuller, P. H.; Kim, J.-W.; Chemler, S. R. *J. Am. Chem. Soc.* **2008**, *130*, 17638.

(44) Donoboe, T. J.; Kabeshov, M. A.; Rathi, A. H.; Smith, I. E. D. *Synlett* **2010**, 2956.

(45) Minakata, S.; Kano, D.; Oderaotoshi, Y.; Komatsu, M. *Org. Lett.* **2002**, *4*, 2097.

(46) Nobuta, T.; Hirashima, S.; Tada, N.; Miura, T.; Itoh, A. *Synlett* **2010**, 2335.

(47) Sels, B. F.; Vos, D. E. D.; Jacobs, P. A. *J. Am. Chem. Soc.* **2001**, *123*, 8350.

Chapter 5

The Reaction of *N*-Acyliminium Ion Pools with Alkenes Having a Nucleophilic Moiety

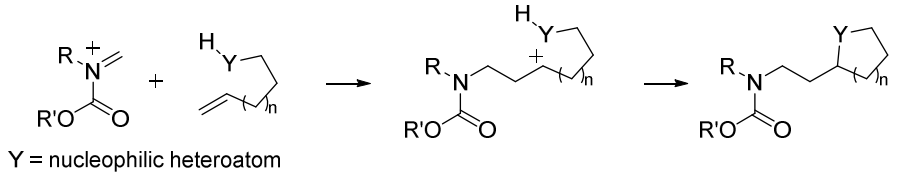
Abstract

The reaction of electrochemically generated *N*-acyliminium ion pools with alkenes bearing a nucleophilic moiety led to intermolecular carbon−carbon bond formation followed by intramolecular carbon−heteroatom bond formation to give the corresponding heterocyclic compounds. The reactions with alkenes bearing a hydroxyl group gave cyclic ethers such as tetrahydrofuran derivatives regio- and stereoselectively. The reactions with alkenes bearing a carboxylic acid moiety gave the corresponding lactones, and those with alkenes bearing an oxime moiety gave the corresponding 2-isoxazolines.

Introduction

Cationic cyclization has emerged as a powerful method for the construction of a variety of biologically important cyclic organic compounds.[1] In particular, cationic cyclization reactions that proceed via *N*-acyliminium ions, which are reactive toward a wide range of nucleophiles,[2] have been extensively utilized in synthesis of nitrogen containing heterocyclic compounds.[3] Recently, sequential domino or cascade type transformations using *N*-acyliminium ions have also been developed.[4] Such reaction integration[5,6] serves as useful methods for construction complex cyclic structures reducing the number of synthetic steps. However, most of such approaches are based on the integration of intramolecular reactions. If intermolecular and intramolecular reactions can be integrated in one sequence, it would serve as powerful methods which are complementary to conventional methods and the scope of cationic cyclization using *N*-acyliminium ions would be expanded to meet demand for synthesis of a variety of nitrogen containing compounds of biological activities (Scheme 1).

Scheme 1. The Reaction of *N*-Acyliminium Ions with Alkenes Bearing a Nucleophilic Heteroatom (Y). Integration of Intermolecular Carbon−Carbon Bond Formation and Intramolecular Carbon−Heteroatom Bond Formation.



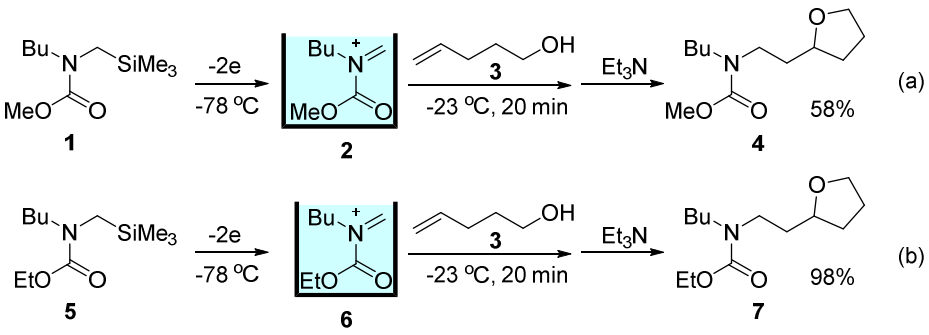
Yoshida and co-workers developed the "cation pool" method[7] based on electrochemical oxidation[8,9] at low temperatures, and the method has been successfully applied to generation and accumulation of *N*-acyliminium ions.[7a,c] The "cation pool" method enables the use of *N*-acyliminium ions as reagents in the solution, which might be suitable for the integration of intermolecular and intramolecular reactions. This chapter shows that *N*-acyliminium ion pools react with alkenes bearing a heteroatom nucleophilic moiety giving rise to intermolecular carbon−carbon bond formation with the one of the carbon atom of olefinic part followed by intramolecular carbon−heteroatom bond formation to give the corresponding heterocyclic compounds.[10]

Results and Discussion

First, the reaction with alkenes bearing a hydroxyl group was investigated.[11] *N*-Acyliminium

ion pool **2**, which was generated by the electrochemical oxidation of carbamate **1** at −78 °C in 0.3 M of Bu_4NBF_4/CH_2Cl_2 solution, was allowed to react with 4-penten-1-ol (**3**) at −23 °C to obtain tetrahydrofuran derivative **4** in 58% yield after work-up with triethylamine (eq a). *N*-Acyliminium ion **2** attacked the terminal olefinic carbon of **3** and the hydroxyl group attacked the other olefinic carbon to give the five-membered ring product selectively (exo cyclization).

On the other hand, the reaction of electrochemically generated *N*-acyliminium ion **6**, which has ethoxycarbamoyl group instead of methoxycarbamoyl group of **2**, with **3** gave the 5-membered ring product **7** in 98% yield (eq b). In both cases, the six-membered ring products which would be formed by the initial attack of **2** on the inner olefinic carbon (endo cyclization) were not detected. The regioselectivity can be explained in terms of the stability of the carbocationic intermediate.

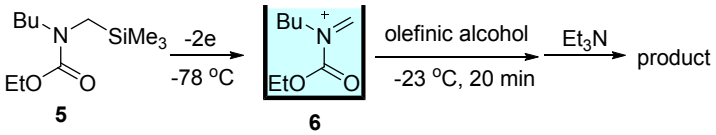


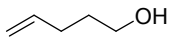
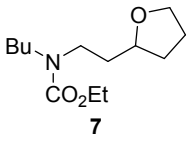
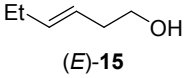
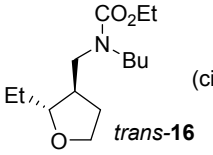
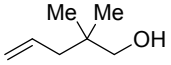
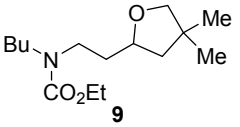
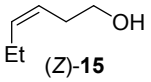
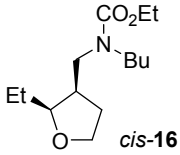
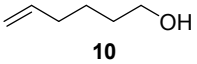
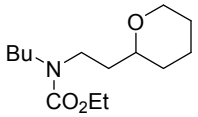
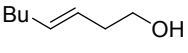
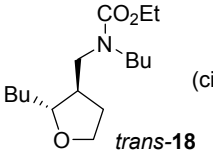
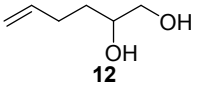
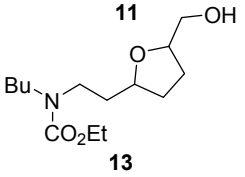
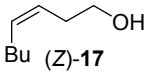
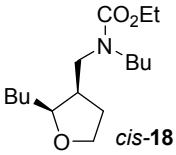
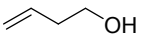
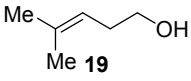
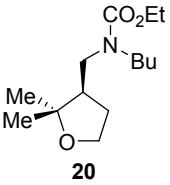
The reactions of **8** also gave the corresponding five-membered ring product **9** in 96% yield (Table 1). In contrast, the reactions with the next higher homologues, 5-hexen-1-ol (**10**) gave the corresponding six-membered ring product **11**, but the yield was low. The reaction of diol **12** gave **13** in 95% yield, indicating that the five-membered ring formation is more favorable than the six-membered ring formation.

The reaction of 3-buten-1-ol (**14**) did not give the corresponding cyclized product. The four-membered ring formation seems to be unfavorable. However, the introduction of an alkyl substituent on the terminal olefinic carbon (**15** and **17**) led to the effective cyclization. Interestingly, *N*-acyliminium ion **6** attacked the olefinic carbon having the hydroxyalkyl tether regioselectively, leading to endo cyclization.

High stereospecificity of the reaction is also notable. For example, the reaction of (*E*)-**15** and (*Z*)-**15** gave *trans*-**16** and *cis*-**16**, respectively in excellent selectivity. Similarly, the reaction of (*E*)-**17** and **(***Z*)-**17** gave *trans*-**18** and *cis*-**18**, respectively in excellent selectivity. The introduction of two alkyl groups on the terminal olefinic carbon did not prevent the reaction. Thus, the reaction of **19** led to effective endo-cyclization to produce **20** in 98% yield.

Table 1. Reactions of *N*-Acyliminium Ion Pool **6** with Olefinic Alcohols.[a]



olefinic alcohol	product	yield(%) [b]	olefinic alcohol	product	yield(%) [b]
 **3**	 **7**	98	 (*E*)-**15**	 *trans*-**16**	93 (cis/trans 1:99)[d]
 **8**	 **9**	96	 (*Z*)-**15**	 *cis*-**16**	89 (cis/trans 99:1)[d]
 **10**	 **11**	23	 (*E*)-**17**	 *trans*-**18**	72 (cis/trans 1:99)[d]
 **12**	 **13**	95[c]	 (*Z*)-**17**	 *cis*-**18**	79 (cis/trans 98:2)[d]
 **14**	complex mixture		 **19**	 **20**	98

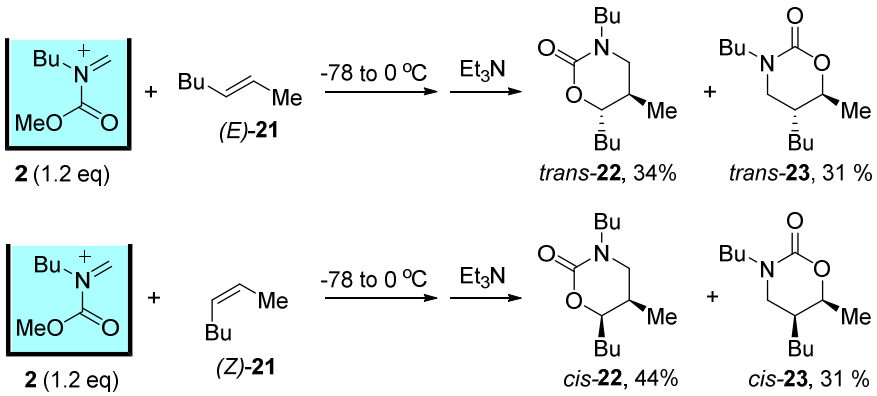
[a]The reactions were carried out with 2 equiv. of **6**, which was generated from 2.5 F/mol of anodic oxidation of **5** using Bu_4NBF_4 as a supporting electrolyte in CH_2Cl_2 at −78 °C, and 1 equiv. of olefinic alkenes at −23 °C for 20 min, and then the reaction was quenched by the addition of triethylamine. [b]Isolated yield. [c]Obtained as 1:1 stereoisomers at 2- and 5-position on the tetrahydrofuran ring. [d]Diastereomer ratio was determined by GC analysis. The stereochemistry of *trans*- and *cis*-**18** was determined by NOE analyses after reduction.

To get a deeper insight into the remarkable regioselectivity and stereospecificity observed for compounds **15** and **17**, the reactions of alkenes bearing an alkoxyalkyl tether instead of a hydroxyalkyl tether were examined. For comparison, the reactions of simple disubstituted alkenes which do not have hydroxyl nor alkoxyl group were examined. Yoshida and co-workers reported that *N*-acyliminium ions having a methoxycarbamoyl group reacted with aliphatic alkenes to give 6-membered-ring products in a stereospecific manner and suggested a concerted [4+2] cycloaddition mechanism based on the computational studies.[4a]

N-acyliminium ion **2** reacted with simple alkene (*E*)-**21** to give a mixture of two regioisomers

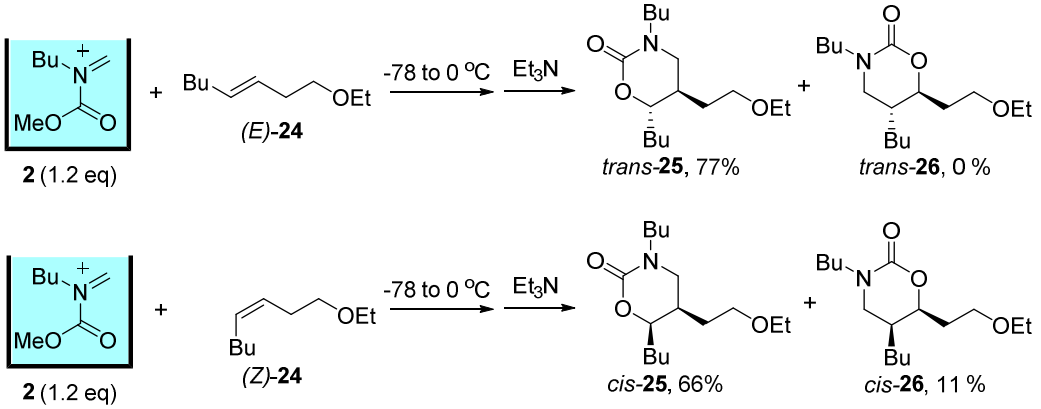
of [4+2] cycloaddition product, *trans*-**22** and *trans*-**23** (Scheme 2). The methyl carbon−oxygen bond in the methoxycarbamoyl group was cleaved during the course of the reaction. The reaction with (*Z*)-**21** also gave a mixture of two regioisomers *cis*-**22** and *cis*-**23**. The high stereospecificity indicated that the reaction proceeded by a concerted mechanism proposed by Yoshida and coworkers. However, the regioselectivity is low.

Scheme 2. The Reactions of *N*-Acyliminium Ion **2** with Simple Dialkyl-Substituted Alkenes **21**.



In contrast, the reaction of **2** with alkene (*E*)-**24**, which has an alkoxyalkyl group, gave *trans*-**25** regioselectively (Scheme 3). The reaction with (*Z*)-**24** gave *cis*-**25** preferentially, although a small amount of *cis*-**26** was also obtained. Because the reaction is stereospecific, a concerted [4+2] cycloaddition mechanism is plausible.

Scheme 3. The Reactions of *N*-Acyliminium Ion **18** with Alkenes Having Alkoxyalkyl Group **22**.



These observations imply that the participation of the oxygen atom of the hydroxyl group is responsible for the remarkable regioselectivity observed for the reaction of *N*-acyliminium ion **6** with **15** and **17** (Figure 1). Transition state for the addition of the *N*-acyliminium ion to the carbon−carbon double bond might be stabilized by the interaction with the hydroxyl group in

TS-A, which leads to the subsequent reaction to form a tetrahydrofuran ring. Such interaction does not effective for regioisomeric TS-B because of smaller ring size. Another possibility to be considered is that the initial [4+2] cycloaddition is reversible and that the participation of the oxygen atom stabilizes one of the regioisomeric intermediates. The intermediate A might be stabilized by the interaction with the hydroxyl group, and the subsequent displacement reaction leads to effective formation of the tetrahydrofuran ring. Such stabilization is not plausible for the regioisomeric intermediate B.

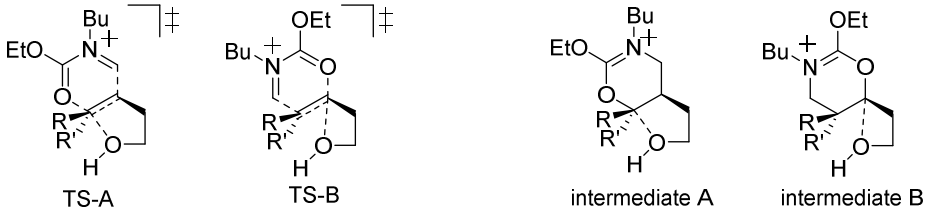


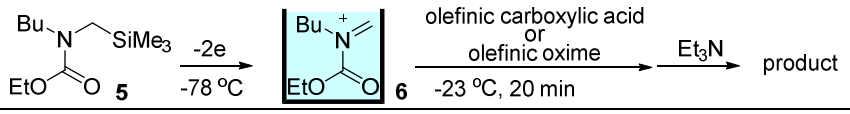
Figure 1. Plausible transition states and intermediates for stereospecific and regioselective reaction of *N*-acyliminium ion **6** with alkenes **15** and **17**.

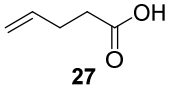
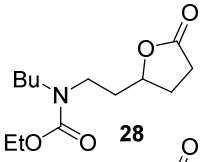
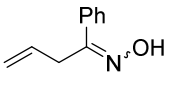
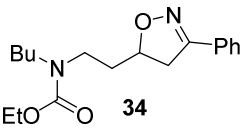
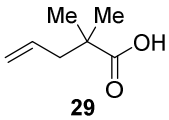
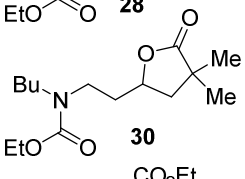
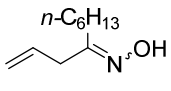
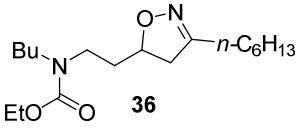
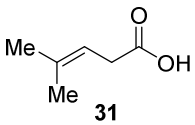
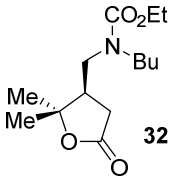
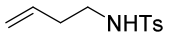
To enhance the synthetic utility of the present method, the reactions of *N*-acyliminium ion pools with alkenes having another heteroatomic nucleophile were studied. At first, the carbolactonization, the reaction of *N*-acyliminium ions with alkenyl carboxylic acids to generate the corresponding cyclized esters, was investigated. *N*-Acyliminium ion **6** was reacted with 4-pentenoic acid (**27**), and the mixture was treated with triethylamine giving the 5-membered lactone **28** in good yield (Table 2). Table 2 shows that 4,4-dimethyl-3-butenoic acid (**29**) also gave exo-cyclization products **30** in high yield. Moreover, the reactions of 4-methyl-3-pentenoic acid (**31**) led to the endo cyclization to give the corresponding γ–lactone **32**.

As shown in Table 2, oximes were also effective as an internal nucleophile of alkenes. *N*-Acyliminium ion pool **6** reacted with alkenes having an oxime moiety (**33** and **35**) gave the products **34** and **36** in moderate yields, which contain a 5-membered unsaturated ring structure having a nitrogen−oxygen bond, 2-isoxazoline ring.[12] Because 2-isoxazolines are precursors for β-hydroxy ketones,[13] β-amino acids,[14] and γ-amino alcohols[15] by cleavage of a nitrogen−oxygen bond, the present reaction serves as a useful method for synthesizing such compounds.

Although there are many examples of intramolecular cyclization of alkenyl tosylamides, this method was not applicable for *N*-tosyl-4-penten-1-amine (**37**). These observations indicate that relatively mild nucleophilicity of oxygenoic groups, such as a hydroxyl group, a carboxylic acid moiety, and an oxime moiety, is suitable for this integration of intermolecular and intramolecular reactions.

Table 2. The Reactions of *N*-Acyliminium Ion **6** with Alkenyl Carboxylic Acids and Oximes.[a]



olefinic carboxylic acid	product	yield(%)[b]	olefinic oxime[c]	product	yield(%)[b]
 **27**	 **28**	67	 **33**	 **34**	55
 **29**	 **30**	84	 **35**	 **36**	44
 **31**	 **32**	71	 **37**	N. D.	

[a]The reactions were carried out with 2 equiv. of **6**, which was generated from 2.5 F/mol of anodic oxidation of **3** using Bu_4NBF_4 as a supporting electrolyte in CH_2Cl_2 at −78 °C, and 1 equiv. of olefinic alkenes at −23 °C for 20 min, and then the reaction was quenched by the addition of triethylamine. [b]Isolated yield. [c]The reaction solution was stirred at 0 °C.

Conclusion

In conclusion, *N*-acyliminium ion pools were found to react with alkenes bearing a hydroxyl group, carboxylic acid moiety, and oxime moiety; the intermolecular carbon−carbon bond formation followed by intramolecular carbon−oxygen bond formation took place, giving the corresponding derivatives of tetrahydrofurans, γ-lactones, and 2-isoxazolines, respectively. The reactions of disubstituted alkenes were stereospecific and regioselective, which could be explained in terms of the participation of the hydroxyl group in the transition state or the intermediate. Because these cyclic architectures play a key role of biologically active natural products and high-performance organic materials, this present method serves as a useful tool for development of functional organic compounds.

Experimental Section

General Remarks. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Varian MERCURY plus-400 (^{1}H 400 MHz, ^{13}C 100 MHz), or JEOL ECA-600P spectrometer (^{1}H 600 MHz, ^{13}C 150 MHz) Chemical shifts are recorded using tetramethylsilane as an internal standard for ^{1}H NMR (0.0 ppm), and methin signal of $CHCl_3$ for ^{13}C NMR (77.0 ppm) unless otherwise noted. Mass spectra were obtained on JEOL EXACTIVE (ESI and APCI), and JEOL JMS-SX102A mass spectrometer (EI). Preparative gel permeation chromatography (GPC) was carried out on Japan Analytical Industry LC-918 equipped with JAIGEL-1H and 2H using $CHCl_3$ as an eluent. Merck precoated silica gel F_{254} plates (thickness 0.25 mm) was used for thin-layer chromatography (TLC) analysis. Flash chromatography was carried out on a silica gel (Kanto Chem. Co., Silica Gel N, spherical, neutral, 40–100 mm). All reactions were carried out under argon atmosphere unless otherwise noted. The anodic oxidation was carried out using an H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon JF-20-P7, ca. 160 mg, dried at 300 ^{o}C/1 mmHg for 3 hours before use) and a platinum plate cathode (10 mm x 10 mm).

Materials. Ethyl butyl(trimethylsilylmethyl)carbamate (**1**),[4a] and (*E*)-3-octen-1-ol ((*E*)-**17**)[16] were prepared according to the reported procedures. Bu_4NBF_4 was purchased from TCI and dried at 50 ^{o}C/1 mmHg for 12 hours. Dichloromethane was washed with water, distilled from P_2O_5, redistilled from dried K_2CO_3 to remove a trace amount of acid, and stored over molecular sieves 4A. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification.

Preparation of cation precursor 5. To a suspension of potassium hydride (35 wt% dispersion in mineral oil, 18.1 g, 157.9 mmol) in DMF (150 mL), *N*-(ethoxycarbonyl)butylamine (15.6 g, 107.4 mmol) was added at 0 ^{o}C. The mixture was stirred for 2 hours at 0 ^{o}C and iodo(trimethylsilyl)methane (64.7 g, 302 mmol) was added at 0 ^{o}C. The reaction mixture was stirred for 2 hours at 60 ^{o}C, and then poured into water (100 mL). The organic phase was separated and the aqueous phase was extracted with ether (100 mL x 3). The combined organic phase was dried over Na_2SO_4, and solvent was removed to give the crude product. The compound was purified by distillation (87.5 ^{o}C, 2.31 mmHg) to obtain **ethyl butyl(trimethylsilylmethyl)carbamate** (**5**) (9.34 g, 38%): TLC R_f 0.29 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 9 H), 0.93 (t, J = 7.2 Hz, 3 H), 1.26 (t, J = 7.2 Hz, 3 H), 1.23−1.37 (m, 2 H), 1.45−1.58 (m, 2 H) 2.70−2.79 (m, 2 H), 3.16−3.25 (m, 2 H), 4.11 (q, J = 7.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.5, 13.8, 14.8, 19.9, 29.5, 37.9 and 38.5, 48.7 and 49.2, 60.9, 156.3; IR (neat) 2959, 1700 cm^{-1}; LRMS (EI) *m/z* 231 [M^+], 216 [$(M-Me)^+$], 186 [$(M-OEt)^+$], 158 [$(M-CO_2Et)^+$]; HRMS (EI) calcd for $C_{11}H_{25}NO_2Si$ [M^+]: 231.1655, found: 231.1655.

Generation of *N*-acyliminium ion pool 6: Typical procedure for *N*-acyliminium ion pools. In the anodic chamber were added ethyl butyl(trimethylsilylmethyl)carbamate (**5**) (694 mg, 3.0 mmol) and 0.3 M Bu_4NBF_4/CH_2Cl_2 (56 mL), and in the cathodic chamber were added trifluoromethansulfonic acid (660 μL, 1.1 g, 7.5 mmol) and 0.3 M Bu_4NBF_4/CH_2Cl_2 (56 mL). The constant current electrolysis (30.0 mA) was carried out at −78 °C with magnetic stirring until 2.5 F/mol of electricity was consumed. The anodic solution (0.06 M at −78 °C) was quickly transferred to a schlenk flusk with argon atmosphere, and stored in a refrigerator.

General procedure for the reactions of an *N*-acyliminium ion pool with alkenes having a nucleophilic moiety. To a solution of nucleophile (0.150 mmol) was added the pool of *N*-acylminium ion **6** (6 mL, cooled at −78 °C) generated from precursor **5** (0.300 mmol), then the mixture was stirred at −23 °C for 20 min. After mixing, the reaction mixture was quenched by addition of Et_3N (0.2 mL) at the same temperature. The mixture was warmed to room temperature. The solvent was removed under reduced pressure and the residue was quickly filtered through a short column (4 x 5 cm) of silica gel to remove Bu_4NBF_4 using diethyl ether as an eluent. The combined solution was concentrated to give a crude product, which was purified by flash chromatography.

Methyl butyl[2-(2-tetrahydrofuranyl)ethyl]carbamate (4). Reaction of **2** (8.0 mL, 0.400 mmol) and 4-penten-1-ol (**3**) (17.6 mg, 0.204 mmol), followed by flash chromatography (hexane/EtOAc 5:1) gave the title compound (58%, 0.119 mmol): TLC R_f 0.12 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J = 7.2 Hz, 3 H), 1.25−1.35 (br, 2 H), 1.41−1.58 (br, 3 H), 1.66−2.04 (m, 6 H), 3.14−3.38 (br, 4 H), 3.67−3.88 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 20.1, 25.7, 30.4 and 30.9, 31.5, 34.2 and 34.8, 44.6 and 45.2, 47.2 and 47.6, 52.3, 67.7, 77.2, 156.6; IR (neat) 2959, 1707 cm^{-1}; LRMS (FAB) *m/z* 230 [M+H$^+$]; HRMS (FAB) calcd for $C_{12}H_{23}NO_3$ [M+H$^+$]: 230.1756, found: 230.1750.

Ethyl butyl[2-(2-tetrahydrofuranyl)ethyl]carbamate (7). Reaction of **6** (5.0 mL, 0.280 mmol) with 4-pentene-1-ol (**3**) (12.8 mg, 0.149 mmol) followed by flash chromatography (hexane/EtOAc 4:1) gave the title compound (98%, 0.146 mmol): TLC R_f 0.31 (hexane/EtOAc 3:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, J = 7.2 Hz, 3 H), 1.25 (t, J = 7.2 Hz, 3 H), 1.24−1.33 (m, 2 H), 1.43−1.58 (m, 3 H), 1.64−1.93 (m, 4 H), 1.97−2.08 (m, 1 H), 3.18−3.38 (m, 4 H), 3.71 (q, J = 8.4 Hz, 1 H), 3.75−3.89 (m, 2 H), 4.09−4.15 (q, J = 7.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.8, 20.1, 25.7, 30.8, 31.5, 34.3, 44.6 and 45.0, 47.1, 60.9, 67.6, 156.1; IR (neat) 2961, 1703 cm^{-1}; LRMS (EI) *m/z* 243 [M$^+$], 216 [(M−Me)$^+$], 186 [(M−OEt)$^+$], 158 [(M−CO_2Et)$^+$]; HRMS (EI) calcd for $C_{13}H_{25}NO_3$ [M$^+$]: 243.1834, found: 243.1834.

Ethyl butyl[2-(4,4-dimethyltetrahydrofuran-2-yl)ethyl]carbamate (9). Reaction of **6** (6.0 mL, 0.300 mmol) and 2,2-dimethyl-4-pentene-1-ol (**8**) (18.6 mg, 0.163mmol), followed by flash chromatography (hexane/EtOAc 3:1) gave the title compound (96%, 0.157 mmol) : TLC R_f 0.34 (hexane/EtOAc 3:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (dt, J = 2.4, 7.2 Hz , 3 H), 1.07 (s, 3 H), 1.08 (s, 3 H), 1.20−1.36 (m, 7 H), 1.46−1.53 (br, 2 H), 1.72−1.84 (br, 2 H), 3.17−3.38 (br, 4 H), 3.40 (d, J = 8.4 Hz, 1 H), 3.49 (d, J = 8.0 Hz, 1 H), 3.95 (br, 1 H), 4.09 (t, J = 7.0 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.7, 14.7, 19.9, 26.5, 26.9, 30.3 and 30.7, 34.8 and 35.3, 39.5, 44.3 and 45.0, 47.4, 60.8, 77.1, 79.9, 156.3; IR (neat) 2957, 1701 cm^{-1}; LRMS (FAB) *m/z* 272 [M+H$^+$]; HRMS (FAB) calcd for $C_{15}H_{30}NO_3$ [M+H$^+$]: 272.2226, found: 272.2224.

Ethyl butyl[2-(2-tetrahydropyranyl)ethyl]carbamate (11). Reaction of **6** (0.408 mmol) and 5-hexene-1-ol (**10**) (34.1 mg, 0.340 mmol), followed by flash chromatography (hexane/EtOAc 10:1) gave the title compound (0.079 mmol, 23%): TLC R_f 0.19 (hexane/EtOAc 10:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, J = 7.2 Hz, 3 H), 1.26 (t, J = 7.2 Hz, 3 H), 1.24−1.34 (m, 2 H), 1.42−1.84 (m, 10 H), 3.12−3.42 (m, 6 H), 3.94−3.98 (m, 1 H), 4.12 (q, J = 7.2 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.9, 14,8, 20.1, 23.6, 26.2, 30.4 and 30.8, 32.1, 35.1 and 35.6, 43.6 and 44.4, 47.0 and 47.4, 60.8, 68.4, 75.6, 156.2; IR (neat) 2959, 1701 cm^{-1}; LRMS (EI) *m/z* 257 [M$^+$], 228 [(M−Et)$^+$], 184 [(M−CO_2Et)$^+$]; HRMS (EI) calcd for $C_{14}H_{27}NO_3$ [M$^+$]: 257.1991, found: 257.1994.

Ethyl butyl[2-(5-hydroxymethyltetrahydrofuran-2-yl)ethyl]carbamate (13). Reaction of **6** (0.521 mmol) and 5-hexene-1,2-diol (**12**) (40.8 mg, 0.351 mmol), followed by flash chromatography (hexane/EtOAc 2:1) gave the title compound as a regio mixture (0.335 mmol, 95%). Major isomer: TLC R_f 0.19 (hexane/EtOAc 2:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, J = 7.4 Hz, 3 H), 1.24−1.36 (br, 5 H), 1.45−1.61 (br, 3 H), 1.62−1.80 (br, 3 H), 1.85−2.09 (br, 4 H), 3.12−3.66 (br, 5 H), 3,67−4.05 (br, 2 H), 4.12 (q, J = 7.2Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.9, 14.7, 20.0, 26.7, 27.5, 30.3 and 30.8, 31.5, 32.1, 33.9 and 34.5, 44.3 and 44.8, 46.9 and 47.3, 60.9, 64.9, 76.8 and 78.8, 77.5 and 79.6, 156.1; IR (neat) 3454, 2969, 1700 cm^{-1}; LRMS (FAB) *m/z* 274 [M+H$^+$]; HRMS (FAB) calcd for $C_{14}H_{28}NO_4$ [M+H$^+$]: 274.2018, found: 274.2016.

Ethyl butyl[(*trans*-2-ethyltetrahydrofuran-3-yl)methyl]carbamate (*trans*-16). Reaction of **6** (5.0 mL, 0.30 mmol) and (*E*)-3-hexen-1-ol ((*E*)-**15**) (13.8 mg, 0.138 mmol), followed by flash chromatography (hexane/EtOAc 10:1) gave the title compound (0.129 mmol, 93%): TLC R_f 0.37 (hexane/EtOAc 3:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88−1.00 (m, 6 H), 1.22−1.28 (m, 3 H), 1.22−1.36 (m, 2 H), 1.41−1.56 (m, 4 H), 1.60−1.74 (m, 1 H), 1.93−2.04 (m, 1 H), 2.10−2.23 (m, 1 H), 3.15−3.38 (m, 4 H), 3.42−3.48 (m, 1 H), 3.77−3.86 (m, 2 H), 4.07−4.15 (q, J = 7.2 Hz, 2

H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 10.4, 13.8, 14.7, 19.9, 27.8, 29.9 and 30.5, 30.7, 42.9 and 43.3, 47.2 and 47.5, 49.2 and 49.8, 61.1, 66.7, 83.6, 156.3 and 156.7; IR (neat) 2961, 1701 cm^{-1}; LRMS (EI) *m/z* 257 [M^+], 242 [$(M-Me)^+$], 228 [$(M-Et)^+$], 212 [$(M-OEt)^+$]; HRMS (FAB) calcd for $C_{14}H_{28}NO_2$ [$M+H^+$]: 257.1991, found: 257.1994. The stereochemistry on the tetrahydrofuran ring was determined by analogy of that of *trans*-**18**.

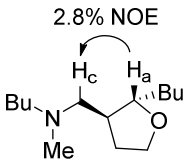
Ethyl butyl[(*cis*-2-ethyltetrahydrofuran-3-yl)methyl]carbamate (*cis*-16). The reaction of **6** (5.0 mL, 0.30 mmol) and (*Z*)-3-hexen-1-ol ((*Z*)-**15**) (14.0 mg, 0.140 mmol), followed by flash chromatography (hexane/EtOAc 5:1) gave the title compound (0.124 mmol, 89%): TLC R_f 0.31 (hexane/EtOAc 3:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.2 Hz, 3 H), 0.99 (t, *J* = 7.2 Hz, 3 H), 1.25 (t, *J* = 7.2 Hz, 3 H), 1.22−1.36 (m, 2 H), 1.40−1.60 (m, 4 H), 1.78−1.86 (m, 1 H), 1.88−1.99 (m, 1 H), 2.39−2.56 (m, 1 H), 3.12−3.33 (m, 4 H), 3.69−3.81 (m, 2 H), 3.90−4.01 (m, 1 H), 4.13 (q, 7.2 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.0, 13.8, 14.7, 20.0, 23.0, 29.0 and 29.3, 30.0 and 30.5, 39.8, 44.8 and 45.7, 47.1 and 47.3, 61.0, 66.0, 82.4, 156.2 and 156.5; IR (neat) 2961, 1701 cm^{-1}; LRMS (EI) *m/z* 258 [$M+H^+$], 257 [M^+], 214 [$(M-OEt)^+$]; HRMS (FAB) calcd for $C_{14}H_{27}NO_3$ [M^+]: 257.1991, found: 257.1991. The stereochemistry on the tetrahydrofuran ring was determined by analogy of that of ***cis*-18**.

Ethyl butyl[(*trans*-2-butyltetrahydrofuran-3-yl)methyl]carbamate (*trans*-18). Reaction of **6** (10.0 mL, 0.59 mmol) and (*E*)-3-octen-1-ol ((*E*)-**17**) (37.1 mg, 0.289 mmol), followed by flash chromatography (hexane/EtOAc 10:1) gave the title compound (72%, 0.209 mmol): TLC R_f 0.35 (hexane/EtOAc 3:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88−0.94 (t, *J* = 7.2 Hz, 3 H), 0.90−0.97 (t, *J* = 7.2 Hz, 3 H), 1.24−1.30 (t, *J* = 7.2 Hz, 3 H), 1.24−1.40 (m, 2 H), 1.40−1.58 (m, 2 H), 1.40−1.58 (m, 2 H), 1.60−1.73 (m, 1 H), 1.97−2.06 (dt, *J* = 7.2, 12.6 Hz, 1 H), 2.10−2.23 (m, 1 H), 3.17−3.38 (m, 4 H), 3.48−3.56 (m, 2 H), 3.76−3.88 (m, 2 H), 4.09−4.18 (q, *J* = 7.2 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.8, 14.0, 14.7, 20.1, 22.7, 28.5, 29.7, 30.7, 34.8, 43.4, 43.8, 47.5, 49.2, 49.8, 61.1, 66.6, 82.4, 156.4.; IR (neat) 2956, 1701 cm^{-1}; LRMS (CI) *m/z* 286 [$M+H^+$], 270 [$(M-Me)^+$], 242 [$(M-OEt)^+$]; HRMS (FAB) calcd for $C_{16}H_{31}NO_3$ [M^+]: 285.2303, found: 285.2305. The stereochemistry of the tetrahydrofuran ring was determined by NOE analysis of *trans*-**38**, which was obtained by reduction of *trans*-**18**.

Butylmethyl(*trans*-2-butyltetrahydrofuran-3-yl)amine (*trans*-38). To a suspension of lithium aluminium hydride (47.9 mg, 1.26 mmol) in THF (1 mL), was added a solution of ethyl butyl[(*trans*-2-butyltetrahydrofuran-3-yl)methyl]carbamate (*trans*-**18**) (59.7 mg, 0.209 mmol) in THF (4 mL). The mixture was stirred for 36 hours at 105 ^{o}C, and then was poured into a 20% solution of potassium sodium tartrate tetrahydrate (10 mL) at room temperature. The organic phase was separated and the aqueous phase was extracted with ether (20 mL x 3). The combined

organic phase was dried over $MgSO_4$, and solvent was removed. The crude product was purified by flash chromatography, hexane/ethyl acetate 3:1 with 1% of Et_3N to obtain the title compound (26.1 mg, 55%): TLC R_f 0.12 (hexane/ethyl acetate 3:1 and 1% Et_3N): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, J = 7.2 Hz, 3 H), 0.91 (t, J = 7.2 Hz, 3 H), 1.22−1.39 (m, 5 H), 1.38−1.52 (m, 4 H), 1.50−1.58 (m, 1 H), 1.58−1.67 (m, 1 H), 1.96−2.10 (m, 2 H), 2.20 (s, 3 H), 2.23−2.38 (m, 4 H), 3.43−3.48 (m, 1 H), 3.70−3.78 (m, 1 H), 3.80−3.87 (m, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.0, 20.6, 22.8, 28.6, 29.4, 29.7, 31.6, 34.9, 42.5, 42.7, 58.0, 61.4, 66.7, 83.5; IR (neat) 2957 cm^{-1}; LRMS (EI) *m/z* 227 [M^+], 184 [$(M-C_3H_7)^+$], 170 [$(M-Bu)^+$]; HRMS [EI] calcd for $C_{14}H_{29}NO$ [M^+]: 227.2249, found: 227.2244.

NOE analysis of *trans*-38. In the NOE experiment of *trans*-**38**, 2.8 % of enhancement of the signal of H_c (attached to the carbon adjacent to the nitrogen) upon irradiation of H_a (attached to the carbon adjacent to the oxygen), in contrast no NOE signal between H_a with H_c was observed from *cis*-**38**, indicating that the butyl group and the aminomethyl group are *trans* to one another.

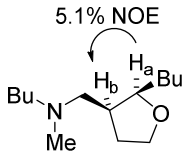


Ethyl butyl[(*cis*-2-butyltetrahydrofuran-3-yl)methyl]carbamate (*cis*-18). Reaction of **6** (10.0 mL, 0.59 mmol) and (*Z*)-3-octen-1-ol ((*Z*)-**17**) (38.0 mg, 0.296 mmol), followed by flash chromatography (hexane/EtOAc 10:1) gave the title compound (79%, 0.233 mmol): TLC R_f 0.32 (hexane/EtOAc 3:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90−0.95 (m, 6 H), 1.22−1.27 (t, J = 7.2 Hz, 3 H), 1.22−1.45 (m, 6 H), 1.38−1.58 (m, 4 H), 1.77−1.86 (m, 1 H), 1.89−1.98 (m, 1 H), 2.35−2.54 (m, 1 H), 3.13−3.32 (m, 4 H), 3.70−3.84 (m, 2 H), 3.90−4.00 (m, 1 H), 4.08−4.17(dd, J = 2.0, 7.0 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.8, 14.1, 14.7, 20.0, 22.8, 29.0, 29.7, 30.5, 40.0, 44.9, 45.8, 47.2 and 47.3, 61.0, 66.0, 80.8, 156.5 and 156.6; IR (neat) 2950, 1705 cm^{-1}; LRMS (FAB) *m/z* 286 [$M+H^+$], 240 [$(M-OEt)^+$]; HRMS (FAB) calcd for $C_{16}H_{31}NO_3$ [M^+]: 285.2303, found: 285.2305. The stereochemistry of the tetrahydrofuran ring was determined by NOE analysis of *cis*-**38**, which was obtained by reduction of *cis*-**18**.

Butylmethyl(*cis*-2-butyltetrahydrofuran-3-yl)amine (*cis*-38). To a suspension of lithium aluminium hydride (49.7 mg, 1.31 mmol) in THF (1 mL), ethyl butyl[(*trans*-2-butyltetrahydrofuran-3-yl)methyl]carbamate (*cis*-**18**) (66.5 mg, 0.233 mmol) was added with THF (4 mL). The mixture was stirred for 36 hours at 105 ^{o}C, and then poured into 20% solution of potassium sodium tartrate tetrahydrate (10 mL) at room temperature. The organic phase was separated and the aqueous phase was extracted with ether (20 mL x 3). The combined organic phase was dried over $MgSO_4$, and solvent was removed to give the crude product. The compound was purified by flash chromatography, hexane/EtOAc 3:1 with 1% of Et_3N to obtain the title

compound (21.5 mg, 41%): TLC R_f 0.12 (hexane/EtOAc 3:1 and 1% Et_3N): ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J = 7.2 Hz, 6 H), 1.25−1.43 (m, 6 H), 1.38−1.47 (m, 5 H), 1.82−2.02 (m, 2 H), 2.19 (s, 3 H), 2.20−2.30 (m, 2 H), 2.30−2.41 (m, 2 H), 3.69−3.77 (m, 1 H), 3.79−3.84 (m, 1 H), 3.86−3.93 (m, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$, one signal was on top of another) δ 14.1, 20.6, 22.9, 29.0, 29.3, 29.5, 30.0, 39.2, 42.6, 56.7, 58.1, 66.0, 81.1; IR (neat) 2957 cm^{-1}; LRMS (CI) *m/z* 228 [M+H$^+$], 227 [M$^+$], 226 [(M−H)$^+$]; HRMS (CI) calcd for $C_{14}H_{29}NO$ [M$^+$]: 227.2249, found: 227.2250.

NOE analysis of *cis*-38. In the NOE experiment of *cis*-**38**, larger enhancement (5.1%) of the signal of H_b upon irradiation of H_a compared with that for *trans*-**38** (0.4%), indicating that the butyl group and the aminomethyl group are *cis* to one another.



Ethyl butyl[(2,2-dimethyltetrahydrofuran-3-yl)methyl]carbamate (20) Reaction of **6** (6.0 mL, 0.300 mmol) and 4-methyl-3-pentene-1-ol (**19**) (16.3 mg, 0.163 mmol), followed by flash chromatography (hexane/EtOAc 5:1) gave the title compound (98%, 0.163 mmol): TLC R_f 0.11 (hexane/EtOAc 5:1): ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, J = 7.2 Hz, 3 H), 1.07 (s, 3 H), 1.25−1.36 (m, 8 H), 1.47−1.63 (m, 2 H), 1.76−1.91 (br, 1 H), 2.03−2.18 (br, 2 H), 3.14−3.29 (br, 4 H), 3.77 (q, J = 8.0 Hz, 1 H), 3.88 (dt, J = 3.2, 8.6 Hz, 1 H), 4.13 (q, J = 7.2 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.7, 14.6, 20.0, 22.0, 27.5, 30.0, 30.5, 30.7, 46.9, 47.5, 61.0, 64.9, 80.7, 156.3 and 156.6; IR (neat) 2966, 1701 cm^{-1}; LRMS (FAB) *m/z* 258 [M+H$^+$]; HRMS (FAB) calcd for $C_{14}H_{28}NO_3$ [M+H$^+$]: 258.2069, found: 258.2069.

Ethyl butyl[2-(5-oxotetrahydrofuran-2-yl)ethyl]carbamate (28). Reaction of **6** (6.0 mL, 0.300 mmol) with 4-pentenoic acid (**27**) (15.2 mg, 0.150 mmol), followed by flash chromatography (hexane/EtOAc 1:1) gave the title compound (67%, 0.102 mmol): TLC R_f 0.27 (hexane/EtOAc 1:1): ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, J = 7.2 Hz, 3 H), 1.27 (t, J = 7.2 Hz, 3 H), 1.25−1.33 (m, 2 H), 1.46−1.54 (m, 2 H), 1.85−2.04 (br, 3 H), 2.34−2.45 (br, 1 H), 2.55 (t, J = 7.2 Hz, 2 H), 3.15−3.30 (br, 2 H), 3.37 (t, J = 7.2 Hz, 2 H), 4.13 (q, J = 7.2 Hz, 2 H), 4.46−4.57 (br, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.8, 14.6, 19.9, 28.0, 28.7, 30.3 and 30.7, 34.3 and 35.0, 44.2 and 43.5, 47.3 and 47.6, 61.1, 78.6, 156.5, 177.0; IR (neat) 2959, 1775, 1669 cm^{-1}; LRMS (FAB) *m/z* 258 [M+H$^+$]; HRMS (FAB) calcd for $C_{13}H_{24}NO_4$ [M+H$^+$]: 258.1705, found: 258.1698.

Ethyl butyl[2-(5-oxo-4,4-dimethyltetrahydrofuran-2-yl)ethyl]carbamate (30). Reaction of **6** (6.0 mL, 0.300 mmol) and 2,2-dimethyl-4-pentenoic acid (**29**) (20.3 mg, 0.150 mmol), followed by flash chromatography (hexane/EtOAc 5:1) and GPC gave the title compound (84%, 0.132

mmol): TLC R_f 0.11 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, J = 7.2 Hz, 3 H), 1.25−1.33 (br, 11 H), 1.46−1.56 (br, 2 H), 1.74−2.06 (m, 3 H), 2.15−2.26 (br, 1 H), 3.14−3.30 (br, 2 H), 3.35−3.38 (br, 2 H), 4.13 (q, J = 7.2Hz, 1 H), 4.38−4.48 (br, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.7, 14.6, 19.8, 24.3, 24.9, 30.2 and 30.7, 34.4 and 35.1, 40.2, 43.4, 44.2, 47.2 and 47.5, 61.0, 74.9 and 74.5, 156.1 and 156.4, 181.6 and 181.7; IR (neat) 2965, 1773, 1698 cm^{-1}; LRMS (FAB) *m/z* 286 [M+H$^+$]; HRMS (FAB) calcd for $C_{15}H_{28}NO_4$ [M+H$^+$]: 286.2018, found: 286.2025.

Ethyl butyl[(5-oxo-2,2-dimethyltetrahydrofran-3-yl)methyl]carbamate (32). Reaction of **6** (6.0 mL, 0.300 mmol) and 4-methyl-3-pentenoic acid (**31**) (17.1 mg, 0.150 mmol), followed by flash chromatography (hexane/EtOAc 1:1) gave the title compound (71%, 0.107 mmol): TLC R_f 0.40 (hexane/EtOAc 1:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.2 Hz, 3 H), 1.26−1.34 (m, 8 H), 1.49−1.54 (m, 5 H), 2.48−2.66 (m, 3 H), 3.10−3.41 (m, 4 H), 4.15 (q, J = 7.2Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.8, 14.6, 19.9, 21.7, 27.4, 30.0 and 30.5, 33.9, 44.4 and 44.6, 46.9 and 47.2, 61.4, 85.2, 155.9 and 156.7, 174.9; IR (neat) 2976, 1778, 1700 cm^{-1}; LRMS (FAB) *m/z* 272 [M+H$^+$]; HRMS (FAB) calcd for $C_{14}H_{25}NO_4$ [M+H$^+$]: 272.1862, found: 272.1866.

Ethyl butyl[2-(3-phenyl-2-isoxazolin-5-yl)ethyl]carbamate (34) Reaction of **6** (5.0 mL, 0.30 mmol) and allylphenylketone oxime (**33**) (23.4 mg, 0.145 mmol), followed by flash chromatography (hexane/EtOAc 4:1 containing 1 vol% of Et_3N) gave the title compound (25.4 mg, 55%): TLC R_f 0.44 (hexane/EtOAc 4:1 containing 1 vol% of Et_3N): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, J = 7.6 Hz, 3 H), 1.24−1.33 (m, 4 H), 1.52 (m, 2 H), 1.96 (m, 2 H), 3.03 (m, 1 H), 3.24 (m, 2 H), 3.34−3.49 (m, 4 H), 4.13 (q, J = 7.2 Hz, 2 H), 4.75 (m, 1 H), 7.39 (m, 3 H), 7.65 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 14.7, 19.9, 29.7, 30.3 and 30.7, 33.9 and 34.6, 40.1, 43.5 and 44.1, 47.2 and 47.6, 61.1, 78.8 and 79.1, 126.6, 128.7, 129.6, 130.0, 156.5; LRMS (EI) *m/z* 319 [M+H$^+$]; HRMS (EI) calcd for $C_{18}H_{26}N_2O_3$ [M$^+$]: 318.1943, found: 318.1947.

Ethyl butyl[2-(3-hexyl-2-isoxazolin-5-yl)ethyl]carbamate (36) Reaction of **6** (5.0 mL, 0.27 mmol) and allylhexylketone oxime (**35**) (24.0 mg, 0.142 mmol), followed by flash chromatography (hexane/EtOAc 5:1) gave the title compound (0.063 mmol, 44%): TLC R_f0.13 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3 H), 0.91 (t, J = 7.2 Hz, 3 H), 1.27−1.35 (m, 6 H), 1.52 (m, 4 H), 1.83 (m, 2 H), 2.32 (t, J = 8.0 Hz, 2 H), 2.48 (m, 1 H), 3.01 (dd, J = 10.0, 16.4 Hz, 1 H), 3.20−3.35 (m, 2 H), 4.11 (q, J = 6.8 Hz, 2 H), 4.53 (m, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.8, 14.0, 14.7, 19.9, 22.5, 26.3, 27.7, 28.9, 30.3, 30.8, 31.4, 33.8, 34.5, 42.3, 43.6, 44.2, 47.2, 47.6, 61.0, 156.5, 159.1; LRMS (EI) *m/z* 326 [M$^+$]; HRMS (EI) calcd for $C_{18}H_{34}N_2O_3$ [M$^+$]: 326.2569, found: 326.2566.

Preparation of (*E*)-1-ethoxy-3-octene ((*E*)-24): General procedure for ethyl ethers. To a stirring suspension of sodium hydride (320 mg, 95% disp. in mineral oil, 13 mmol) in 100 mL THF at 0 °C, (*E*)-3-octen-1-ol ((*E*)-**17**) (522 mg, 4.1 mmol) was slowly added. After stirring for 1 hour at 0 °C, ethyl iodide (1.53 g, 9.8 mmol) was slowly added to the yellow cloudy reaction mixture, and it was slowly warmed to room temperature. After 80 min at room temperature, the reaction mixture was refluxed for 11 hours. The reaction was cooled and quenched with saturated brine solution. The layers were separated and the aqueous phase was extracted with ether (20 mL x 3). The combined organic phase was dried over $MgSO_4$, and solvent was removed to give the crude compound. Flash chromatography (hexane/EtOAc 20:1) of crude mixture gave the title compound (456 mg, 72%): TLC R_f 0.33 (hexane/EtOAc 20:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 7.2 Hz, 3 H), 1.18 (t, J = 7.2 Hz, 3 H), 1.22−1.37 (m, 2 H), 1.93−2.02 (m, 4 H), 2.22−2.29 (m, 2 H), 3.40 (t, J = 7.2 Hz, 2 H), 3.46 (q, J = 7.2 Hz, 2 H), 5.34−5.52 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 15.1, 22.1, 31.6, 32.3, 33.1, 66.0, 70.5, 126.1, 132.5; IR (neat) 2959 cm^{-1}; LRMS (FAB) *m/z* 157 [M+H$^+$], 155 [(M-H)$^+$]; HRMS (FAB) calcd for $C_{10}H_{21}O$ [M+H$^+$]: 157.1587, found: 157.1587.

(*Z*)-1-Ethoxy-3-octene ((*Z*)-24). Reaction of sodium hydride (0.851 g, 95% disp. in mineral oil, 35 mmol), (*Z*)-3-octen-1-ol ((*Z*)-**17**) (3.54 g, 28 mmol), and ethyl iodide (5.23 g, 34 mmol) followed by flash chromatography (hexane/EtOAc 15:1) gave the title compound (2.48 g, 57%): TLC R_f 0.27 (hexane/ethyl acetate 20:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J = 7.2 Hz, 3 H), 1.20 (t, J = 6.8 Hz, 3 H), 1.25−1.40 (m, 4 H), 2.00−2.08 (m, 2 H), 2.31−2.38 (m, 2 H), 3.41 (t, J = 7.2 Hz, 2 H), 3.49 (q, J = 7.2 Hz, 2 H), 5.32−5.41 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.0, 15.2, 22.3, 27.0, 28.0, 31.8, 66.1, 70.3, 125.4, 132.0; IR (neat) 2959 cm^{-1}; LRMS (EI) *m/z* 156 [M$^+$], 141 [(M−Me)$^+$], 111 [(M−OEt)$^+$]; HRMS (EI) calcd for $C_{10}H_{20}O$ [M$^+$]:156.1514, found: 156.1517.

General procedure for [4+2] cycloaddition reactions. To a solution of a nucleophile (0.417 mmol) in CH_2Cl_2 (10 mL, cooled at −78 °C), *N*-acylminium ion pool **2** (10 mL, cooled at −78 °C) generated from ethyl butyl(trimethylsilylmethyl)carbamate (0.500 mmol) was added by a syringe pump (flow rate, 5.0 mL/min). At this time the solution of **2** were quickly transferred to syringes, which were kept cool with dry ice, thus decomposition of **2** was avoided. After 10 minutes, the solution warmed to 0 °C then stirred for 10 min before quenching by addition of Et_3N (1 mL) at the same temperature. After quenching the mixture was warmed to room temperature and the solvent was removed under reduced pressure. The residue was quickly filtered through a short column (10 cm) of silica gel to remove Bu_4NBF_4. The silica gel was washed with ether (300 mL). The combined solution was concentrated to give a crude product, which was purified by flash chromatography.

***trans*-3,6-Dibutyl-5-methyl-[1,3]oxazinan-2-one (*trans*-22).** Reaction of **2** (10.0 mL, 0.540 mmol) with (*E*)-2-heptene ((*E*)-**21**) (46.5mg, 0.473 mmol), followed by flash chromatography (hexane/EtOAc 3:1) gave the title compound in 34% yield (36.2 mg, 0.159 mmol). TLC R_f 0.44 (hexane/EtOAc 1:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 7.2 Hz, 3 H), 0.91 (t, J = 7.2 Hz, 3 H), 0.95 (d, J = 6.8 Hz, 3 H), 1.22−1.44 (m, 5 H), 1.46−1.60 (m, 4 H), 1.61−1.73 (m, 1 H), 1.87−1.99 (m, 1 H), 2.93 (dd, J = 10.4, 11.2 Hz, 1 H), 3.16 (dd, J = 5.6, 10.8 Hz, 1 H), 3.19−3.25 (m, 1 H), 3.31−3.41 (m, 1 H), 3.80−3.88 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 13.9, 14.2, 19.9, 22.6, 26.3, 29.1, 30.9, 32.0, 48.8, 51.5, 81.7, 153.8; IR (neat) 2959, 1698 cm^{-1}; LRMS (EI) *m/z* 227 [M^+], 212 [$(M-Me)^+$], 198 [$(M-Et)^+$]; HRMS (EI) calcd for $C_{13}H_{25}NO_2$ [M^+]: 227.1885, found: 227.1890.

***trans*-3,5-Dibutyl-6-methyl-[1,3]oxazinan-2-one (*trans*-23).** The title compound was generated and isolated as above in 31% yield (32.8 mg, 0.144 mmol). TLC R_f 0.30 (hexane/EtOAc 1:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85−0.95 (m, 6 H), 1.09−1.20 (m, 1 H), 1.23−1.36 (m, 6 H), 1.32 (d, J = 6.4 Hz, 3 H), 1.45−1.61 (m, 3 H), 1.67−1.77 (m, 1 H), 2.96 (dd, J = 10.0, 12.8 Hz, 1 H), 3.18−3.27 (m, 2 H), 3.33−3.42 (m, 1 H), 4.01−4.07 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 13.8, 19.0, 19.9, 22.7, 28.5, 29.0, 29.1, 37.8, 49.0, 49.5, 77.3, 153.5; IR (neat) 2957, 1698 cm^{-1}; LRMS (EI) *m/z* 227 [M^+], 212 [$(M-Me)^+$], 198 [$(M-Et)^+$]; HRMS (EI) calcd for $C_{13}H_{25}NO_2$ [M^+]: 227,1885, found: 227.1880.

***cis*-3,6-Dibutyl-5-methyl-[1,3]oxazinan-2-one (*cis*-22).** Reaction of **2** (10.0 mL, 0.540 mmol) with (*Z*)-2-heptene ((*Z*)-**21**) (44.7mg, 0.455 mmol), followed by flash chromatography (hexane/EtOAc 3:1) gave the title compound in 44% yield (45.1mg, 0.198 mmol): TLC R_f 0.41 (hexane/EtOAc 1:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86−0.96 (m, 6 H), 0.94 (d, J = 6.8 Hz, 3 H), 1.23−1.39 (m, 5 H), 1.40−1.58 (m, 4 H), 1.58−1.65 (m, 1 H), 2.03−2.14 (m, 1 H), 2.95 (dd, J = 4.0, 11.6 Hz, 1 H), 3.21−3.36 (m, 2 H), 3.42 (dd, J = 5.2, 10.4 Hz, 1 H), 4.16−4.21 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.3, 13.8, 13.9, 19.9, 22.5, 27.4, 29.1, 29.1, 30.9, 48.9, 51.6, 79.4, 153.3; IR (neat) 2959, 1696 cm^{-1}; LRMS (EI) *m/z* 227 [M^+], 212 [$(M-Me)^+$], 198 [$(M-Et)^+$], 170 [$(M-Bu)^+$]; HRMS (EI) calcd for $C_{13}H_{25}NO_2$ [M^+]: 227.1885, found: 227.1886.

***cis*-3,5-Dibutyl-6-methyl-[1,3]oxazinan-2-one (*cis*-23).** The title compound was isolated as above in 32% yield (32.6 mg, 0.143 mmol): TLC R_f 0.34 (hexane/EtOAc 1:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, J = 6.8 Hz, 3 H), 0.92 (t, J = 7.6 Hz, 3 H), 1.25 (d, J = 6.4 Hz, 3 H), 1.27−1.37 (m, 8 H), 1.48−1.58 (m, 2 H), 1.99−2.07 (m, 1 H), 3.08 (dd, J = 8.4, 12.0 Hz, 1 H), 3.17−3.26 (m, 2 H), 3.32−3.41 (m, 1 H), 4.37−4.45 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 13.8, 15.4, 19.9, 22.6, 26.7, 29.1, 29.2, 35.3, 47.6, 49.1, 75.2, 153.2; IR (neat) 2957, 1697

cm^{-1}; LRMS (EI) *m/z* 227 [M^+], 212 [$(M-Me)^+$], 170 [$(M-Bu)^+$]; HRMS (EI) calcd for $C_{13}H_{25}NO_2$ [M^+]: 227.1885, found: 227.1877.

***trans*-3,6-Dibutyl-5-(2-ethoxyethyl)-[1,3]oxazinan-2-one (*trans*-25).** Reaction of **2** (10.0 mL, 0.540 mmol) with (*E*)-1-ethoxy-3-octene ((*E*)-**24**) (41.0 mg, 0.473 mmol), followed by flash chromatography (hexane/EtOAc 2:1) gave the title compound in 77% yield (57.7 mg, 0.202 mmol): TLC R_f 0.31 (hexane/ethyl acetate 1:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87−0.97 (m, 6 H), 1.20 (t, *J* = 7.2 Hz, 3 H), 1.24−1.40 (m, 5 H), 1.40−1.75 (m, 6 H), 1.78−1.84 (m, 1 H), 1.95−2.06 (m, 1 H), 3.00−3.08 (dd, *J* = 8.4, 11.6 Hz, 1 H), 3.20−3.30 (m, 1 H), 3.32−3.41 (m, 2 H), 3.42−3.51 (m, 4 H), 3.96−4.03 (m, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.0, 14.0, 15.3, 20.0, 22.6, 26.6, 29.2, 29.7, 32.4, 33.1, 48.8, 49.0, 66.3, 67.5, 80.4, 153.2; IR (neat) 2957, 1698 cm^{-1}; LRMS (EI) *m/z* 285 [M^+], 270 [$(M-Me)^+$], 256 [$(M-Et)^+$]; HRMS (FAB) calcd for $C_{16}H_{31}NO_3$ [$M+H^+$]: 285.2304, found: 285.2301.

***cis*-3,6-Dibutyl-5-(2-ethoxyethyl)-[1,3]oxazinan-2-one (*cis*-25).** Reaction of **2** (10.0 mL, 0.540 mmol) with (*Z*)-1-ethoxy-3octene ((*Z*)-**24**), followed by flash chromatography (hexane/EtOAc 5:1) gave the title compound in 66% yield (85.2 mg, 0.298 mmol): TLC R_f 0.39 (hexane/EtOAc 1:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87−0.95 (m, 6 H), 1.19 (t, *J* = 6.8 Hz, 3 H), 1.28−1.39 (m, 5 H), 1.43−1.58 (m, 5 H), 1.56−1.81 (m, 2 H), 2.13−2.23 (m, 1 H), 3.16 (dd, *J* = 5.6, 11.8 Hz, 1 H), 3.25−3.35 (m, 3 H), 3.42−3.50 (m, 4 H), 4.20−4.28 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 13.9, 15.1, 19.9, 22.5, 25.6, 27.6, 29.1, 30.1, 32.3, 48.5, 49.1, 66.3, 68.2, 79.5, 153.3; IR (neat) 2957, 1698 cm^{-1}; LRMS (EI) *m/z* 285 [M^+], 270 [$(M-Me)^+$], 256 [$(M-Et)^+$]; HRMS (EI) calcd for $C_{16}H_{31}NO_3$ [M^+]: 285.2304, found: 285.2303.

***cis*-3,5-Dibutyl-6-(2-ethoxyethyl)-[1,3]oxazinan-2-one (*cis*-26).** The title compound was isolated as above in 11% yield (13.9 mg, 0.049 mmol). TLC R_f 0.27 (hexane/EtOAc 1:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83−0.93 (m, 6 H), 1.16 (t, *J* = 7.2 Hz, 3 H), 1.23−1.37 (m, 5 H), 1.42−1.59 (m, 5 H), 1.55−1.74 (m, 2 H), 2.13−2.21 (m, 1 H), 3.13 (dd, *J* = 6.8, 11.6 Hz, 1 H), 3.21−3.34 (m, 3 H), 3.40−3.46 (m, 4 H), 4.17−4.23 (m, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.8, 13.8, 15.1, 19.9, 22.4, 25.9, 27.5, 29.1, 30.0, 32.2, 48.5, 49.0, 66.2, 68.1, 79.5, 153.3; IR (neat) 2957, 1698 cm^{-1}; LRMS (EI) *m/z* 285 [M^+], 256 [$(M-Et)^+$]; HRMS (EI) calcd for $C_{16}H_{31}NO_3$ [M^+]: 285.2303, found: 285.2303.

References

(1) Reviews for cationic cyclizations: (a) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321. (b) Snyder, S. A.; Treitler, D. S.; Brucks, A. P. *Aldrichim. Acta* **2011**, *44*, 27.

(2) (a) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431. (b) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311.

(3) Martínez-Estibalez, U.; Gómez-SanJuan, A.; Garcia-Calvo, O.; Aranzamendi, E.; Lete, E.; Sotomayor, N. *Eur. J. Org. Chem.* **2011**, 3610.

(4) (a) Suga, S.; Nagaki, A.; Tsutsui, Y.; Yoshida, J. *Org. Lett.* **2003**, *5*, 945. (b) Suga, S.; Kageyama, Y.; Babu,G.; Itami, K.; Yoshida, J. *Org. Lett.* **2004**, *6*, 2709. (c) Suga, S.; Nishida, T.; Yamada, D.; Nagaki, A.; Yoshida, J. *J. Am. Chem. Soc.* **2004**, *126*, 14338. (d) Suga, S.; Tsutsui, Y.; Nagaki, A.; Yoshida, J. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 1206. (e) Sarkar, N.; Banerjee, A.; Nelson, S. G. *J. Am. Chem. Soc.* **2008**, *130*, 9222. (f) Suga, S.; Yamada, D.; Yoshida, J. *Chem. Lett.* **2010**, *39*, 404. (g) Rohlmann, R.; Stopka, T.; Richter, H.; Mancheño, O. G. *J. Org. Chem.* **2013**, *78*, 6050.

(5) Reviews: (a) Schmidt, B. *Pure Appl. Chem.* **2006**, *78*, 469. (b) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861. (c) Yoshida, J.; Saito, K.; Nokami, T.; Nagaki, A. *Synlett* **2011**, 1189.

(6) Recent examples: (a) Ashikari, Y.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2011**, *133*, 11840. (b) Kim, H.; Nagaki, A.; Yoshida, J. *Nat. Commun.* **2011**, *2*, 264. (c) Fuchibe, K.; Jyono, H.; Fujiwara, M.; Kudo, T.; Yokota, M.; Ichikawa, J. *Chem.−Eur. J.* **2011**, *17*, 12175. (d) Mitamura, Y.; Yorimitsu, H.; Oshima, K.; Osuka, A. *Chem. Sci.* **2011**, *2*, 2017. (e) Fuse, S.; Mifune, Y.; Tanabe, N.; Takahashi, T. *Org. Biomol. Chem.* **2012**, *10*, 5205. (f) Mitsudo, K.; Kamimoto, N.; Murakami, H.; Mandai, H.; Wakamiya, A.; Murata, Y.; Suga, S. *Org. Biomol. Chem.* **2012**, *10*, 9562. (g) Ashikari, Y.; Nokami, T.; Yoshida, J. *Org. Lett.* **2012**, *14*, 938. (h) Asano, K.; Matsubara, S. *Org. Lett.* **2012**, *14*, 1620. (i) Murata, T.; Murai, M.; Ikeda, Y.; Miki, K.; Ohe, K. *Org. Lett.* **2012**, *14*, 2296. (j) Ashikari, Y.; Nokami, T.; Yoshida, J. *Org. Biomol. Chem.* **2013**, *11*, 3322. (k) Pünner, F.; Hilt, G. *Eur. J. Org. Chem.* **2013**, 5580.

(7) Selected examples: (a) Yoshida, J.; Suga, S.; Suzuki, S.; Kinomura, N.; Yamamoto, A.; Fujiwara, K. *J. Am. Chem. Soc.* **1999**, *121*, 9546. (b) Suga, S.; Suzuki, S.; Yamamoto, A.; Yoshida, J. *J. Am. Chem. Soc.* **2000**, *122*, 10244. (c) Yoshida, J.; Suga, S. *Chem.−Eur. J.* **2002**, *8*, 2650. (d) Nokami, T.; Ohata, K.; Inoue, M.; Tsuyama, H.; Shibuya, A.; Soga, K.; Okajima, M.; Suga, S.; Yoshida, J. *J. Am. Chem. Soc.* **2008**, *130*, 10864. (e) Okajima, M.; Soga, K.; Watanabe, T.; Terao, K.; Nokami, T.; Suga, S.; Yoshida, J. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 594: An example of radical cation pools, see: (f) Morofuji, T.; Shimizu, A.; Yoshida, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 7259.

(8) (a) Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527. (b) Sperry, J. B.; Wright, D. L. *Chem. Soc. Rev.* **2006**, *35*, 605. (c) Yoshida, J.; Kataoka, K.; Horcajada, R.; Nagaki, A. *Chem. Rev.* **2008**, *108*, 2265.

(9) Recent examples: (a) Bours, J.; Morton, M.; Fry. A. J. *Tetrahedron Lett.* **2012**, *53*, 1015. (b) Zeng, C.-c.; Zhang, N.-t.; Lam, C. M.; Little, R. D. *Org. Lett.* **2012**, *14*, 1314. (c) Dai, J.-J.; Huang, Y.-B.; Fang, C.; Guo, Q.-X.; Fu, Y. *ChemSusChem* **2012**, *5*, 617. (d) Kirste, A.; Elsler, B.; Schnakenburg, G.; Waldvogel, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 3571. (e) Ishiguro, Y.; Inagi, S.; Fuchigami, T. *J. Am. Chem. Soc.* **2012**, *134*, 4034. (f) Finney, E. E.; Ogawa, K. A.; Boydston, A. J. *J. Am. Chem. Soc.* **2012**, *134*, 12374. (g) Sumi, K.; Saitoh, T.; Natsui, K.; Yamamoto, T.; Atobe, M.; Einaga, Y.; Nishiyama, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 5443. (h) Shida, N.; Ishiguro, Y.; Atobe, M.; Fuchigami, T.; Inagi, S. *ACS Macro Lett.* **2012**, *1*, 656. (i) Yamaguchi, Y.; Okada, Y.; Chiba, K. *J. Org. Chem.* **2013**, *78*, 2826. (j) Morofuji, T.; Shimizu, A.; Yoshida, J. *J. Am. Chem. Soc.* **2013**, *135*, 5000.

(10) An example of phenonium cation promoted olefin cyclization; Protti, S.; Dondi, D.; Fagnoni, M.; Albini, A. *Eur. J. Org. Chem.* **2008**, 2240.

(11) Some examples of an alkenyl alcohol cyclization involving a carbon−carbon bond formation using transition metal catalysts: (a) Nakhla, J. S.; Kampf, J. W.; Wolfe, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 2893. (b) Zhang, G.; Cui, L.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 1474. (c) Jensen, K. H.; Webb, J. D.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 17471.

(12) Jiang, D.; Peng, J.; Chen, Y. *Org. Lett.* **2008**, *10*, 1695.

(13) (a) Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826. (b) Andersen, S. H.; Sharma, K. K.; Torssell, K. B. G. *Tetrahedron* **1983**, *39*, 2241. (c) Bode, J. W.; Fraefel, N.; Muri, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 2082. (d) Jiang, D.; Chen, Y. *J. Org. Chem.* **2008**, *73*, 9181.

(14) (a) Minter, A. R.; Fuller, A. A.; Mapp, A. K. *J. Am. Chem. Soc.* **2003**, *125*, 6846. (b) Fuller, A. A.; Chen, B.; Minter, A. R.; Mapp, A. K. *J. Am. Chem. Soc.* **2005**, *127*, 5376.

(15) (a) Marotta, E.; Micheloni, L. M.; Scardovi, N.; Righi, P. *Org. Lett.* **2001**, *3*, 727. (b) Scott, J. P.; Oliver, S. F.; Brands, K. M. J.; Brewer, S. E.; Davies, A. J.; Gibb, A. D.; Hands, D.; Keen, S. P.; Sheen, F. J.; Reamer, R. A.; Wilson, R. D.; Dolling, U. *J. Org. Chem.* **2006**, *71*, 3086. (c) Jager, V.; Schroter, D. *Synthesis* **1990**, 556.

(16) Rossi, R.; Carpita, A. *Synthesis* **1977**, 561.

List of Publications

1. Integrated Electrochemical−Chemical Oxidation Mediated by Alkoxysulfonium Ions
   Ashikari, Y.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2011**, *133*, 11840−11843.
   (Chapter 1 and 2)

2. Integration of Electrooxidative Cyclization and Chemical Oxidation via Alkoxysulfonium Ions. Synthesis of Exocyclic Ketones from Alkenes with Cyclization
   Ashikari, Y.; Nokami, T.; Yoshida, J. *Org. Biomol. Chem.* **2013**, *11*, 3322−3331.
   (Chapter 2)

3. Oxidative Hydroxylation Mediated by Alkoxysulfonium Ions
   Ashikari, Y.; Nokami, T.; Yoshida, J. *Org. Lett.* **2012**, *14*, 938−941.
   (Chapter 3)

4. Halogen and Chalcogen Cation Pools Stabilized by DMSO. Versatile Reagents for Alkene Difunctionalization
   Ashikari, Y.; Shimizu, A.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* in press. DOI: 10.1021/ja4092648
   (Chapter 4)

5. Addition of *N*-Acyliminium Ion Pools to Alkenes Having a Nucleophilic Moiety: Integration of Intermolecular and Intramolecular Reactions
   Ashikari, Y.; Kiuchi, Y.; Takeuchi, T.; Ueoka, K.; Suga, S.; Yoshida, J. *Chem. Lett.* accepted.
   (Chapter 5)

Other Publications

1. Electro-initiated Coupling Reactions of *N*-Acyliminium Ion Pools with Arylthiomethylsilanes and Aryloxymethylsilanes
   Suga, S.; Shimizu, I.; Ashikari, Y.; Mizuno, Y.; Maruyama, T.; Yoshida, J. *Chem. Lett.* **2008**, *37*, 1008−1009.

2. Electrophilic Substitution Reactions Using an Electrogenerated $ArS(ArSSAr)^+$ Cation Pool as an ArS^+ Equivalent
   Matsumoto, K.; Kozuki, Y.; Ashikari, Y.; Suga, S.; Kashimura, S.; Yoshida, J. *Tetrahedron Lett.* **2012**, *53*, 1916−1919.

3. The Addition of ArSSAr to Alkenes: The Implication of a Cationic Chain Mechanism Initiated by Electrogenerated $ArS(ArSSAr)^+$
   Matsumoto, K.; Sanada, T.; Shimazaki, H.; Shimada, K.; Hagiwara, S.; Fujie, S.; Ashikari, Y.; Suga, S.; Kashimura, S.; Yoshida, J. *Asian J. Org. Chem.* **2013**, *2*, 325−329.

4. Recent Development in the "Cation Pool" Method
   Yoshida, J.; Ashikari, Y.; Matsumoto, K.; Nokami, T. *J. Synth. Org. Chm., Jpn.* **2013**, *71*, in press.